Thesis for MD degree

Assessment of cerebral oxygenation using near infra red spectroscopy in obstructive sleep apnoea and chronic obstructive pulmonary disease

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Abstract

This thesis describes a set of studies of the use of near infrared spectroscopy to measure cerebral oxygenation in obstructive sleep apnea (OSA) and chronic hypoxia. Cerebral oxygenation depends on cerebral blood flow and arterial oxygen saturation. The hypothesis underlying these studies was whether measurement of cerebral oxygenation using near infra-red spectroscopy (NIRS) gives additional valid information compared to measuring arterial oxygen saturation alone. We also hypothesized that this technique could be used to assess overnight cerebral oxygenation in sleep studies.

Our first validation study in 13 subjects with significant OSA showed that the fall in cerebral tissue saturation (measured as tissue oxygenation index, TOI) during sleep apnoea is related to arterial saturation (SaO_2) ($p=0.012$), apnoea duration ($p=0.001$) and sleep stage ($p<0.001$) in a multiple regression in 1036 apnoeas. We also demonstrated changes in cerebral blood volume (range 0.41 - 0.09 ml/100g) and cytochrome oxidase oxidation state (range 0.48 - 0.13μM) occurring during apnoeas in 8 of these subjects.

In a second validation study in 8 subjects we demonstrated correlations between changes in TOI and both arterial saturation ($p=0.001$), apnoea duration ($p=0.001$) and cerebral blood flow velocity ($p=0.012$) measured using carotid Doppler.

We derived area under the curve (AUC) measures and dip rates for TOI and SaO2 during overnight studies and compared them to conventional polysomnographic measures, showing significant correlations of pretreatment apnoea hypopnoea index (AHI) with dip rates for both TOI and SaO2. AUC TOI correlations with pretreatment AHI were weak. Mean AUC for TOI was 339.4 (161-675) and mean AUC for SaO_2 was 308.5 (89-944). Mean 4% SaO_2 dip rate was 32.6 (1.5-90.6) and mean 4% TOI dip rate was 24 (0.1-95.7).

Pilot studies were also carried out on 11 subjects with chronic obstructive pulmonary disease (COPD) during oxygen challenge. Calculated cerebral blood volume measurements varied from 1.51 ml/100g to 3.65 ml/100g. Changes in TOI in response to supplementary oxygen in patients with COPD and chronic hypoxia are related to both cerebral blood volume ($p=0.001$) and arterial saturation ($p=0.001$).

The most important new findings in these studies are that cerebral blood flow changes appear to exacerbate rather than compensate for arterial hypoxia during sleep apnoea, and so it is plausible that TOI measurement (which picks up both SaO_2 and cerebral blood flow velocity (CBFV) changes) may be more closely related to changes in

neuropsychological function than pulse oximetry. The changes in cerebral oxygenation are profound enough to affect intracerebral redox state measured as cytochrome oxidase oxidation. Pilot work in COPD patients suggests that changes in cerebral blood volume affecting cerebral oxygenation occur during supplementary oxygen administration. NIRS provides a non-invasive method of measuring cerebral oxygenation suitable for use in sleep studies, and during oxygen administration.

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1. BACKGROUND TO THE THESIS

1.1 ABBREVIATIONS

ABG arterial blood gas
ABP arterial blood pressure
ADC analogue to digital converter
AHI apnoea hypopnoea index
AI arousal index
ATP adenosine triphosphate
AUC area under the curve

BMI body mass index

C3/A2, C4/A1 EEG positions
CBFV cerebral blood flow velocity
CBF cerebral blood flow
CBV cerebral blood volume
CPAP continuous positive airway pressure
CO_2 carbon dioxide
COPD chronic obstructive pulmonary disease
CSF cerebrospinal fluid
Ctox cytochrome oxidase
CVP central venous pressure

2,3 DPG 2,3diphosphoglycerate
DPF differential pathlength factor

ECA external carotid artery

ECG electrocardiogram

EEG electroencephalogram

Elpsec elapsed seconds

EMG electromyogram

ENT ear nose and throat

EOG electro-oculogram

Et CO_2 end tidal carbon dioxide

Hb haemoglobin

Hbdiff difference between oxy and deoxyhaemoglobin concentrations

HHb deoxyhaemoglobin

Hhbthbmax value of Hhb at maximum total haemoglobin

Hhbthbmin value of Hhb at minimum total haemoglobin

ICA internal carotid artery

ICP intracranial pressure

IPPB intermittent positive pressure breathing

IOS intra optode space

ITU intensive therapy unit

Km substrate concentration at which an enzyme is 50% saturated

LDF laser doppler flowmetry

LTOT long term oxygen therapy

MCA middle cerebral artery

MRC medical research council

MRI magnetic resonance imaging

MRS magnetic resonance spectroscopy

NIR near infra-red

NIRS near infra-red spectroscopy

NIRO near infra-red oximeter

NOTT nocturnal oxygen therapy trial

Ohb Oxyhaemoglobin

Ohbratio proportion of oxyhaemoglobin in the total haemoglobin change during apnoea

Ohbthbmax value of Ohb at maximum total haemoglobin

Ohbthbmin value of Ohb at minimum total haemoglobin

OSA obstructive sleep apnoea

pCO_2 partial pressure of carbon dioxide

PET positron emission tomography

pet CO_2 partial pressure of carbon dioxide (end tidal)

pO2 partial pressure of oxygen

R&K Rechtschaffen and Kales

RDI respiratory disturbance index (event rate measured without EEG)

REM rapid eye movement

rSO2 regional saturation measured by INVOS NIR spectrometer

SaO_2 arterial oxygen saturation

SCI severe cerebral ischaemia

SIT saturation impairment time

SjO2 Jugular bulb oxygen saturation

SPECT single photon emission computed tomography

SRS spatially resolved spectroscopy

T90 Time (in a sleep study) spent with SaO_2 <90%

TCD trans cranial doppler

THb Total haemoglobin

TipO2 tissue oxygen concentration

TOI tissue oxygenation index

UARS upper airway resistance syndrome

UCL University College, London

UCLH University College, London, Hospitals

VQ ventilation perfusion

1.2 STATEMENT OF INVOLVEMENT

This thesis on the use of near infrared spectroscopy to measure cerebral oxygenation in respiratory disease includes data from two validation studies in OSA subjects, a prospective study using objective neuropsychological testing, and pilot studies in COPD subjects. Professor Spiro, Head of the Department of Respiratory Medicine, supervised my MD, and supported the sleep research work with regular meetings.
Professor L'Estrange (sleep prosthodontist, Middlesex Hospital) made the initial contact with Clare Elwell in the Department of Medical Physics and Bioengineering and performed a pilot study on one patient in her department, before I joined the sleep unit.

1.2.1 Validation study 1

I was not involved in the data recording of the initial 8 patients, which was performed by Dr Himender Makker, Consultant in Respiratory Medicine UCLH, Arschang Valipour, Visiting Research Fellow, and Stephen Emegbo, sleep technician. With Arschang I was involved in recruitment and data recording of the subsequent OSA patients, and data processing and analysis as reported in chapter 7. Statistical advice was provided by Caiomhe O'Sullivan from UCL. I was responsible for the final revision of the paper prior to publication (1) because Dr Valipour was no longer working in the department.
I was entirely responsible for data processing and analysis of the cytox and CBV traces as reported in chapter 8, published in Sleep (2), following initial advice from Clare Elwell on presentation of data.

1.2.2 Validation study 2

On the advice of Prof Delpy (Department of Medical Physics and Bioengineering, UCL) I contacted Mr Kirkpatrick at Department of Neurosurgery, Addenbrookes (who had done the initial pilot work on NIRO300 which was awaiting publication), and was invited to give a presentation of our pilot work in Cambridge. Following this he offered us the necessary collaboration for Validation study 2, which included the loan of Pippa Al Rawi, research physiologist, experienced in Doppler CBFV measurement. I wrote

the protocol, obtained ethical approval and recruited subjects for this study with the support of Dr Makker and Professor Spiro. Pippa and I performed the study. The data was collected onto a database held by Pippa, I subsequently obtained a copy and performed the analysis reported in chapter 9.

1.2.3 Prospective neuropsychological study.

This was performed in collaboration with the Unit of Health Psychology UCL, led by Professor Stanton Newman, with whom I made contact with an initial one page proposal. The protocol was co-ordinated by me, with input from Prof Spiro, Dr Makker, Jan Stygall (research psychologist), Prof Newman, Prof Harrison (Professor of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square) and Prof Delpy (Department of Medical Physics and Bioengineering, UCL). Grant applications and the ethical application were submitted by me. The research clinic was set up by Dr Makker and the two of us recruited patients. Kerri Mellehan was employed as an additional sleep technician to enable the study to continue recruiting during my period of maternity leave. Osler tests were performed by myself, Kerri Mellehan (sleep technician) and Chris Smith (sleep technician). Neuropsychological testing was performed by Jan Stygall, Jane Harrington and Shashi Hirani, all psychologists from the Unit of Health Psychology. Screening sleep studies were performed routinely by Kanta Gajria (lead sleep technician), Kerri Mellehan (sleep technician), Chris Smith (sleep technician). Research polysomnographies were performed by me, Kerri Mellehan, Chris Smith and Ming Luo (previous research registrar). CPAP titration was performed routinely by the sleep technicians, compliance was read by me and the sleep technicians if necessary. Polysomnographies were staged by Kerri Mellehan or myself. All TOI analysis on polysomnography and digital output was performed by myself, following piloting of the methods used to calculate summary measures on the data from validation study 1 by myself and Arschang Valipour.
The neuropsychological database was held by the Unit of Health Psychology. All polysomnography analysis was performed blind to neuropsychological outcome and no neuropsychological results are reported in this thesis.

1.2.4 COPD pilot studies

I wrote the protocol for these with advice from Prof Delpy and support from Dr Makker. I wrote the ethics submission and recruited patients. The studies were performed with Arschang Valipour and we analysed the data together.

1.3 PUBLICATIONS ARISING FROM THE THESIS

1.3.1 Publications arising from this Thesis (peer-reviewed)

Arschang Valipour, Anne D McGown , Himender Makker, Caiomhe O'Sullivan, Stephen G Spiro. Some factors affecting cerebral tissue saturation during obstructive sleep apnoea. *European Respiratory Journal* 2002 **20** 444-450

Anne D McGown, Himender Makker, Clare Elwell, Pippa Al Rawi, Arschang Valipour,Stephen G Spiro. Measurement of changes in cytochrome oxidase redox state during obstructive sleep apnoea using near infra-red spectroscopy. *Sleep* 2003 **26** 710-16

1.3.2 Published abstracts arising from this thesis:

Valipour A, Makker H, Emegbo S, McGown A, Smith C, Spiro S.
Cerebral oxygenation in patients with obstructive sleep apnoea. *Am J Respir Crit Care Med* 2000 **161** A483

McGown AD, Valipour A, Makker HK, Emegbo S, Delpy DT and Spiro SG
Measurement of changes in cytochrome oxidase redox state during obstructive sleep apnoea using near infrared spectroscopy. *Eur Resp J* 2000 **16** (S31) p168s P1220

Valipour A, McGown AD, O'Sullivan C, Makker HK and Spiro SG.
Non-invasive measurements of regional cerebral oxygenation during sleep in subjects with obstructive sleep apnoea (OSA). *Thorax* 2000; **55** (Suppl 3) A24

McGown AD, Valipour A, Makker HK and Spiro SG
Measurement of cerebral oxygenation during oxygen challenge in chronic obstructive pulmonary disease (COPD) using near infra-red spectroscopy. *Thorax* 2000; **55** (Suppl

3) A40

McGown AD, Al-Rawi PG, Makker HK, Spiro SG, Kirkpatrick PJ.
Cerebral oxygenation monitoring during obstructive sleep apnoea reflects changes in cerebral blood flow velocity as well as arterial oxygen saturation changes. *Eur Resp J* 2002 **20**(S38) p295s P1867

Harrington J, McGown A, Stygall J, Hirani S, Makker H, Spiro SG, Harrison M, Newman S. The association between oxygen desaturation dip rate in obstructive sleep apnoea and neuropsychological function. *Sleep Medicine* 2003 **4** (S1) S17

McGown AD, Makker HK, Stygall J, Harrington J, Smith C, Mellehan K, Spiro SG. Relationship between polysomnographic measures of sleep fragmentation and hypoxaemia and measures of daytime sleepiness in consecutive patients with obstructive sleep apnoea referred to a sleep clinic. *Thorax* 2003 **58** (suppl III) S16 (oral presentation at the BTS Winter Meeting 2003)

McGown A, Harrington J, Stygall J, Makker H, Hirani S, Harrison M, Spiro SG, Newman S. Cerebral oxygenation during REM sleep in obstructive sleep apnoea is associated with daytime neuropsychological function. *Eur Resp J* 2004 **24** (Suppl 48) 444s P2742.

2. INTRODUCTION

Oxygen is necessary for all the cells in the body for the metabolism of fats and carbohydrates to produce energy for anabolic processes and cellular protein function. The brain is particularly susceptible to oxygen deprivation because of its rapid metabolic rate and inability to metabolise fatty acids, making it more reliant on mitochondrial aerobic respiration. Oxygen enters the blood through the nose and mouth via the gas exchange interface of the lungs. Diseases of the upper and lower respiratory tract may limit oxygen supply to the bloodstream. Pathological patterns of hypoxia include repetitive dips in obstructive sleep apnea (OSA) and constant compensated hypoxia in respiratory failure in chronic obstructive pulmonary disease (COPD). These naturally occurring models of hypoxia enable the effects of oxygen lack on the brain to be studied in humans, given appropriate validated non-invasive instruments to assess continuous cerebral oxygenation. Near infrared spectroscopy (NIRS) is a technique for non-invasive study of tissue oxygenation which has been available for about 20 years. This thesis describes preliminary studies of cerebral oxygenation in OSA and hypoxic COPD using near infra-red spectroscopy.

2.1 HISTORICAL PERSPECTIVE

Obstructive sleep apnoea is often considered to be a modern disease of the western world, but descriptions of cases of respiratory obstruction during sleep in association with daytime hypersomnolence are found in the nineteenth century literature. Without any formal overnight monitoring, these case studies are detailed observations of patients while asleep. The first description of mixed sleep apnoea was by Broadbent in 1877: "*When a person, especially advanced in years, is lying on his back in heavy sleep and snoring loudly, it very commonly happens that every now and then the inspiration fails*

to overcome the resistance in the pharynx of which stertor or snoring is the audible sign, and there will be perfect silence through two, three, or four respiratory periods, in which there are ineffectual chest movements; finally air enters with a loud snort, after which there are several compensatory deep inspirations before the breathing settles down to its usual rhythm. In the case to which I allude there was something more than this. The snoring ceased at regular intervals, and the pause was so long as to excite attention, and indeed alarm; and I found, on investigation, that there was not simply obstruction by the falling back of the tongue & c, but actual cessation of all respiratory movements; these then began gradually, but did not at first attain sufficient force to overcome the pharyngeal resistance." (from (3)). Two further cases were described in 1889, one by Richard Caton "*The thorax and abdomen are seen to heave from fruitless contractions of inspiratory and expiratory muscles; their efforts increase in violence for about a minute or a minute and a half, the skin meantime becoming more and more cyanosed, until at last, when the condition to the onlooker is most alarming, the glottic obstruction yields, a series of long inspirations and expirations follows, and cyanosis disappears. This acute dyspnoeic attack does not wake the patient.*" and one by Morison " *I have myself observed him asleep in bed with an intensely cyanotic countenance, a condition from which he was roused after a snorting and choking sound had issued from his respiratory passages, the cyanosis then gradually disappearing*"(3). Both these two case studies included descriptions of excessive daytime sleepiness, the former, a poulterer, falling asleep while serving customers, and the latter falling asleep while playing cards, and dropping his cards on the table. These detailed descriptions of obstructive sleep apnoea are instantly recognizable to those of us who have used video sleep study systems (where often the video alone suffices for diagnosis), however then (as now among lay people) there was confusion as to whether "bad snoring" was actually pathological. When these descriptions were made, the nature and purpose of sleep was yet to be described, and the sleep state was deemed to be one of inactivity and lack of stimulation, defined behaviourally. Sleepiness was not considered a serious symptom. All subjects with what was considered pathological sleepiness were lumped together under the term narcolepsy. Major developments in the twentieth century were the development of polysomnography and the formal description of the Pickwickian syndrome as a case study (4). Sleep studies on Pickwickian patients followed, leading to the definitions of the sleep apnoea syndromes as distinct from the Pickwickian syndrome.

The first EEG (electroencephalogram) was recorded in 1929 by Berger (5). Kleitman in Chicago pioneered the study of sleep electroencephalography in the 1930s and 40s (6). Initial descriptions of eye movements during sleep were observational, electro-oculography was then added to the system. These studies were completed using paper records, and initially intermittent recording was the norm because of the quantity of paper produced by continuous nocturnal recording. In 1957, Dement and Kleitman (7) described sleep stages organized in cyclic periods repeated 3-5 times a night, each one being completed by a period of desynchronized EEG and rapid eye movement sleep. Demonstration that electromyographic activity was completely suppressed during REM sleep followed in 1962 (8). The standard scoring manual for sleep staging was published in 1968 (9). Development of transistor technology allowing digitalization of multichannel data simplified storage problems. By 1972 the recording of respiratory and cardiac variables as part of the all-night sleep test (later called polysomnography) became routine, originating in Dement's laboratory in Stanford (10). It is against this background of sleep studies taking place in research neurophysiology laboratories, that sleep apnoea emerged as a new diagnosis.

Charles Dickens describes a "wonderfully fat boy" with excessive daytime sleepiness in the Pickwick papers in 1837 (Figure 1).

Figure 1. Thomas Nast's drawing of the fat boy in "The Pickwick Papers"(4).

The term Pickwickian syndrome was used by Burwell in 1956 (4) to describe a case of an obese 51 year old business executive with daytime hypersomnolence, daytime cyanosis and cor pulmonale. Table 1 gives the clinical features of the Pickwickian syndrome as defined by this one case.

Table 1. Clinical features of the Pickwickian syndrome (4)

1	Obesity, marked
2	Somnolence
3	Twitching
4	Cyanosis
5	Periodic respiration
6	Polycythemia, secondary
7	Right ventricular hypertrophy
8	Right ventricular failure

No sleep studies were performed on this case, and pulmonary function testing suggested a diagnosis of alveolar hypoventilation. Although this description is not of an uncomplicated sleep apnoea patient the term Pickwickian was subsequently used to describe the association of sleepiness and obesity. Jung and Kuhlo (11) performed sleep studies on three subjects with the Pickwickian syndrome and demonstrated apnoeas during sleep in 1965. These apnoeas were terminated by arousals and the subjects rarely reached slow wave sleep. This together with a second description by Gastaut (12) constitute the first polysomnographic descriptions of sleep apnoea. The cause of the apnoeas was thought to be an abnormal central response to hypercapnia, and hypercapnia was also blamed for the sleepiness initially.

The Stanford University Sleep Disorders Clinic was set up in 1970 and accepted referrals predominantly of subjects with excessive daytime sleepiness as possible narcolepsy. Between June 1972 and June 1975 62 subjects with sleep apnoea syndromes were diagnosed from approximately 350 referrals (13). The common clinical picture of loud snoring, abnormal behaviour during sleep, nocturnal enuresis, morning headaches and daytime sleepiness was then described. Even at this stage poor correlation between sleep apnoea severity and daytime symptoms was observed, and

various mechanisms were postulated for the daytime symptoms, including sleep deprivation from repetitive sleep disturbance and a defect in the CNS structures that control sleep. The defining parameters of obstructive sleep apnoea were published in 1976. Since then some treatments that reduce upper airway obstruction have been developed: initially tracheostomy, then nasal continuous positive airway pressure (CPAP), mandibular advancement devices and certain ENT procedures. None of the treatments that reverse the anatomical problem are simple and compliance is a major issue in both CPAP and dental devices. There is also a stimulant tablet modafinil which has been used to treat residual daytime symptoms in subjects compliant with CPAP (14) and has a central alerting effect without any effect on the obstruction.
It is important to define the rationale for treatment and the adverse effects of the various physiological changes which occur during OSA so that the right choices are made about who should be treated.

2.2 PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNOEA

2.2.1 Definitions

Sleep apnoea is a condition characterized by episodic absence of airflow during sleep. Obstructive sleep apnoea occurs due to transient closure of the upper airway during sleep. A clinical diagnosis of OSA requires a specified rate of obstructive episodes per hour usually with symptoms.

2.2.2 Physiology of upper airway collapse

The primary occurrence in obstructive sleep apnoea is collapse of the oropharyngeal airway during sleep. There is a fall in pharyngeal dilator tone during sleep in all people. Other common factors contributing to upper airway collapse are obesity and facial anatomy, in particular retrognathism. Neck circumference predicts OSA (15), so distribution of fat around the neck rather than just BMI is important in pathogenesis. Rarely, enlarged tonsils, pharyngeal tumours, endocrine disorders eg hypothyroidism or acromegaly and congenital conditions such as the mucopolysaccharidoses may increase risk of OSA in adults. Airway collapse is more common in the supine position, and muscle relaxation is increased by alcohol and hypnotic drugs.

2.2.3 Apnoeas and hypopnoeas

Severity of OSA is measured by an event rate, classically the apnoea hypopnoea index or sum of apnoeas and hypopnoeas per hour. Episodes of complete (apnoea) and partial (hypopnoea) obstruction cause similar physiological effects. An apnoea is defined as absence of oronasal airflow for 10 seconds (16). Hypopnoeas have been variously defined, most commonly as a reduction in tidal volume to less than 50% of the previous values. The currently accepted definition for use in research studies is an airflow reduction of >50% compared to a 10s peak amplitude during the preceding 2 min, lasting>=10s and associated with either oxygen desaturation of >=3s or an arousal (16).

2.2.4 Effects on blood gas concentrations

Airway obstruction causes a fall in the partial pressure of oxygen in the alveoli, which results in a fall in arterial oxygen saturation with magnitude dependent on how steep the oxygen dissociation curve is at the starting point. There is similarly a rise in carbon dioxide. The extent of desaturation depends on lung volume at start of apnoea, underlying lung disease, sleep stage and duration of apnoea.

2.2.5 Effects on intrathoracic pressure

Attempts by the respiratory muscles to overcome the obstruction cause a reduction in intrathoracic pressure which may go as low as –100cmH2O. These pressure changes distinguish obstructive from central apnoeas, and affect cardiac output and venous return.

2.2.6 Apnoea termination and arousal

The rise in carbon dioxide may trigger the chemoreceptors to initiate respiration again, as may intrathoracic pressure changes acting on pulmonary stretch receptors. Apnoeas are terminated by arousal from a deeper to a lighter stage of sleep or wakefulness. Arousal is defined as 3 or more seconds of a significant change in the EEG (17). Arousal is accompanied by sympathetic stimulation, catecholamine release and an increase in arterial blood pressure. An arousal index of arousals per hour may be calculated and is the best measure of sleep disturbance from polysomnography. The threshold for arousal varies with sleep stage and is highest in REM sleep. At the moment of arousal the activity of the upper airway dilator muscles returns. The airway

often opens suddenly with a snorting noise.

2.2.7 Serial apnoeas

A brief period of hyperventilation follows arousal. This may lead to hypocapnia and a fall in respiratory drive initiating further airway collapse and a series of repetitive apnoeas.

2.2.8 Effects on heart rate

A brief bradycardia may accompany apnoea due to the diving reflex. Sympathetic outflow causes tachycardia accompanying arousal. Arrhythmias, may arise secondary to a combination of catecholamines and hypoxia, particularly in those with underlying ischaemic heart disease.

2.2.9 Effects on blood pressure

Cardiac output and blood pressure are reduced during apnoea due to the intrathoracic negative pressure, and then arousal causes an abrupt rise in arterial blood pressure due to sympathetic activation. Blood pressure then falls back again for the next apnoea.

2.2.10 Effects on cerebral blood flow

The effects on cerebral blood flow will be described in detail because of their bearing on cerebral oxygenation, which depends on arterial saturation and blood flow to the brain.

Cerebral blood flow in subjects with obstructive sleep apnoea has been previously assessed in a number of studies, mainly using Doppler cerebral blood flow velocity (CBFV)(18-24), but also radioisotope techniques (25). During each obstructive apnoea CBFV both reduces below baseline (frequently by 50% or more) (22) and then increases above baseline (eg by as much as 110%) (24). Factors affecting CBFV during an apnoea include the passive effect of reduced intrathoracic pressure, blood pressure changes during arousal, and hypercapnoea and hypoxia as part of an autoregulatory response. Evidence for a role in intrathoracic pressure in the reduction of CBFV in obstructive apnoeas comes from the fact that a significant (50%) decline in CBFV occurred in 76% of 223 obstructive hypopnoeas and 80% of obstructive apnoeas, compared with only 14% of central apnoeas (22). Balfors and Franklin showed a close correlation between systemic blood pressure changes and CBFV changes ($r = 0.67$,

$p<0.001$), initially increasing after apnoea, then decreasing below baseline (18). A blood pressure surge accompanies autonomic arousal at the end of an apnoea, and this systemic blood pressure increase appears to be transmitted to the cerebral circulation. Evidence that normal autoregulation does not operate as usual on this time scale also comes from a study of cerebral haemoglobin concentrations in spontaneously breathing volunteers (26). A role for hypercapnoea in the cerebral blood volume increase is suggested by the similarity between the CBFV traces in OSA and in voluntary apnoeas in healthy subjects (24); a direct relation between mean flow velocity increase and end-tidal pCO_2 in 10 patients (20), and a similar relation between endapneic transcutaneous pCO_2 and mean CBFV in one subject (24 apnoeas) (23). Subjects with severe OSA may have a blunted CBF response to hypercapnoea (27), although this finding has not always been replicated (28).

2.2.11 Effects on intracranial pressure

Changes in intracranial pressure (ICP) have also been observed during apnoeas. ICP has been measured in 3 patients with OSA by Sugita et al (29), who observed a marked episodic elevation of CSF pressure peaking at the end of each apnoea. They correlated the increase in pressure with apnoea duration and oxygen saturation dip. ICP elevation must be secondary to either an increase in CVP, an increase in ABP or hypoxic/hypercapnoeic vasodilatation increasing CBF (as the blood compartment is the only compartment that can change in volume on this timescale). A more detailed study by Jennum and Borgesen (30)showed a gradual increase in ICP during each apnoea, associated with an increase in pCO_2 and a decrease in pO2, and then an abrupt further increase associated with an increase in ABP at the end of the apnoea. These two studies are generally in agreement with the findings using Doppler CBFV, and suggest that the observed changes in CBFV are true changes in CBF, rather than being related to changes in vessel calibre.

2.3 CLINICAL INVESTIGATION

As described above the initial descriptions of sleep apnoea were made in neurophysiology laboratories which had been primarily designed to investigate

neuropsychiatric sleep disorders. Polysomnography was defined as the gold standard investigation for OSA before the causes and consequences of the spectrum of sleep disordered breathing were fully described. Hence new sleep study systems have all been validated against polysomnography rather than against clinical endpoints. The main physiological changes as detailed above include changes in airway resistance, respiratory muscle activity, heart rate, blood pressure, blood gas tensions and sleep interruption. Polysomnography using electroencephalogram (EEG), electromyogram (EMG), electrooculogram (EOG), oro-nasal flow, strain gauge plethysmography and pulse oximetry, enables characterization of sleep interruption using EEG arousals, as well as defining apnoeas and hypopnoeas and distinguishing central and obstructive events. It does not allow measurement of upper airway resistance. It is time consuming both to set up and to analyse. Correlations between classic polysomnography and daytime symptoms are poor, so although all sleep study equipment is validated against the polysomnography-derived apnoea hypopnoea index (AHI), it can be argued that this measure has never been properly validated itself as a measure of clinical sleep apnoea severity. However it does allow sleep staging which gives information on sleep quality and rapid eye movement (REM) sleep specific apnoea.

Screening sleep studies may be based on oximetry alone and are reliable when clinical probability is high. Oximetry combined with some way of measuring obstruction (eg sound recording of snoring or video) is commonly used for screening (31, 32). These systems lack methods of characterizing sleep interruption. There has been recent interest in using autonomic methods of characterizing arousals, for example heart rate or blood pressure measurements. Continuous non-invasive blood pressure monitoring is uncomfortable and so the pulse transit time is increasingly being used instead (33). Pulse transit time is the time taken for the initial blood pressure shock wave to pass from the opened aortic valve to the periphery and depends on blood pressure. It can therefore be used to identify arousals in association with apnoeas.

The other group of new sleep study techniques attempt to characterize upper airway narrowing and inspiratory effort. These include sleep nasendoscopy, measurement of nasal flow, oesophageal pressure monitoring, and measurement of paradoxical ribcage and abdominal movements. Information about intrathoracic pressure can also be derived from blood pressure and pulse transit time measurements (32).

To summarise, the move away from polysomnography to simpler systems brings into focus the poor correlations between event rates and day time symptoms. There is a need

for more information about the neurophysiological basis of the symptoms of sleep apnoea so that we measure the right things and treat the right people. Hence our interest in measuring cerebral oxygenation in OSA to see whether it predicts daytime function better than measurements based on pulse oximetry or sleep interruption.

2.4 CLINICAL CONSEQUENCES OF OSA

2.4.1 Sleepiness

The main presenting daytime symptom of obstructive sleep apnoea is sleepiness. The two early descriptions in the 1880s described the occupational and social consequences of this problem (3). In addition the medicolegal consequences of falling asleep at work were first referred to in 1909 in the case of a post boy: "*The chief interest in this case, from his master's point of view, is the possibility of an accident..... If an accident occurred under these circumstances, his employer might have an action of damage brought against him. He is probably insured against such risks; but his insurance company, if they knew that his employer was aware of the fact that the patient is apt to go to sleep on the box, might naturally dispute the claim.*" The recent Selby rail crash where a car came off a motorway onto a railway track in the UK has served as a reminder to those who work in sleep clinics of the legal attitude to people that drive when sleepy. Objective measurement of sleepiness was initially performed using the Multiple Sleep Latency Test, defined by Mary Carskadon in 1975 (34). Maintenance of wakefulness tests are probably more relevant in the sleep apnoea population and both EEG based and behavioural versions have been standardized. The Osler test is a behavioural maintenance of wakefulness test where the subject is asked to stay awake in a darkened room and activate a touch sensitive button in response to a red light which comes on every 3s. It has been validated against the traditional polysomnography based MWT and is simpler to perform (35). Driving simulation tests eg Steerclear are also used in evaluation of OSA subjects. For routine clinic monitoring of sleepiness, validated sleep questionnaires for example the Epworth sleepiness scale are commonly used (36).

2.4.2 Blood pressure and cardiovascular risk

After many years of debate evidence is now emerging that OSA is an independent risk factor for hypertension. Cross-sectional studies show an increased prevalence of hypertension in subjects with OSA (13). Because hypertension and OSA share common risk factors, it has been difficult to say whether OSA actually causes hypertension. The most important common risk factor is central obesity which is often poorly measured in studies, and contributes to vascular risk more than overall obesity does (37). Attempts can be made to reduce the effect of a common risk factor by using carefully matched controls in a case control study or by careful statistical adjustment in cohort studies. A case control study matching 45 patients with moderate to severe OSA with 45 controls showed increased ambulatory diastolic blood pressure both day and night and increased systolic blood pressure at night (38). A prospective cohort study of 709 subjects demonstrated a dose response association between sleep disordered breathing and the presence of hypertension 4 years later that was independent of known confounders (39). A recent review of 53 non-interventional studies supports this independent association between OSA and hypertension (40). If sleep apnoea causes hypertension then treating sleep apnoea should reduce blood pressure. Six randomised controlled trials of the effects of treatment on blood pressure are summarised in the review quoted previously (40). Some of these trials suggest benefit of CPAP (41, 42), and others do not (43, 44). Overall CPAP seems to produce a measurable reduction in BP in more severe OSA cases with excessive daytime sleepiness, but not in mild cases in the absence of EDS. This conflicts with the observational evidence that mild OSA is associated with raised BP in the community (39, 45), suggesting either that the clinical trials are underpowered or that some of the BP difference is not CPAP responsive.

Obstructive sleep apnoea may be associated with an increased stroke risk over and above that predicted by the blood pressure changes. Studies of patients presenting with stroke have shown that snoring (46) and sleep apnoea (47) are common. Fifty-three percent of 55 consecutive stroke patients had an AHI of greater than 10, compared with 11% seen in control populations (47). Studying the association in incident stroke cases is complicated by the fact that stroke may cause sleep apnoea because of effects on upper airway tone. Pharyngeal dysfunction is common after cerebral and brainstem strokes (48), and measured OSA event rates decrease with time following a stroke (49). Attempts to determine the pathway of causation have included looking at stroke

recurrence (50); a case control study of transient ischaemic attack where there is no neurological deficit (51); and a longitudinal population study of stroke incidence (52). Patients with stroke recurrence had a higher AHI than patients with first ever stroke (50), however there was no evidence of an increase in OSA in TIA patients compared with community-matched controls (51). In the prospective study sleep disordered breathing with an AHI >20 was associated with an increased risk of suffering a first ever stroke over the next 4 years (unadjusted odds ratio 4.31 (CI 1.31-14.15); adjusted odds ratio 3.08 (CI 0.74 – 12.81) (52). This is probably the first prospective evidence that sleep disordered breathing precedes stroke and may contribute to stroke causation. The quartet of risk factors: systemic hypertension, insulin resistance, hyperlipidaemia and central obesity (syndrome X, now the metabolic syndrome) are often found in association with OSA (53) and are a major risk factor for ischaemic heart disease (54, 55). The pattern of central and upper body obesity associated with OSA (15) is that that carries the highest cardiovascular risk (55). One study comparing OSA subjects with controls suggests that OSA is independently associated with an increase in the cardiovascular risk factors that constitute the metabolic syndrome (56). There may be specific effects of OSA for example on blood viscosity, sympathetic drive and vascular endothelial function which further increase the cardiovascular consequences of this risk factor association (53).

2.4.3 Other health effects

There are also improvements in quality of life after treatment with CPAP (57, 58). One small non-randomised trial in 1988 suggested survival benefit on treatment.

2.4.4 Neuropsychological function in OSA

We are interested in studying cerebral oxygenation in OSA because of the well-described but poorly explained effects of OSA on neuropsychological function. Neuropsychological impairment is common in patients with OSA. Most patients complain of both excessive daytime sleepiness and cognitive impairment (59). Their driving competence and mood are also impaired. However, the mechanism of neuropsychological impairment in OSA is not known. The two main proposed causes are disturbed sleep and hypoxia. Various studies have attempted correlation between sleep study parameters eg AHI, extent of nocturnal hypoxia and arousal index; and

aspects of neuropsychological performance, both before and after treatment.

Correlation between sleep study parameters and impaired day time performance.

Disturbed sleep does not seem to explain all the deficit, and correlations between hypoxaemia and cognitive deficit seem to be consistent. Cheshire et al (60) found that nocturnal hypoxaemia is more closely correlated with cognitive deficit than oxygenation while awake, and demonstrated that the frequency of apnoeas and hypopnoeas is independently associated with specific and global cognitive impairment in 29 patients. Bedard et al (61) in 20 OSA patients and 10 controls showed that attention performance was related to sleepiness, and IQ and executive function related to hypoxaemia. Kotterba et al (62) in 31 OSA patients and 10 controls showed impairment of alertness, selective attention and continuous attention with no effect on vigilance, and showed that cognitive deficits correlated with the degree of nocturnal hypoxaemia. Naegele et al (63) using logistic regression correlated memory deficits with AHI and frontal lobe related abnormalities with nocturnal hypoxaemia in 17 subjects with OSA compared to 17 controls. A larger study of 150 subjects with daytime sleepiness showed significant but weak (r^2 <0.1) relationships between several nocturnal measures (AHI, AI and desaturation variables) and daytime measures of cognitive performance (64). A systematic review of studies of neuropsychological function in sleep disordered breathing has recently been published (65).

Treatment studies.

Neuropsychological deficits appear to be partially reversible with treatment. In the study of Kotterba et al (62) alertness and continuous attention improved significantly after 6 mths of treatment, but persistence of some neuropsychological deficits could be demonstrated relative to the control group. CPAP had been used for 5.4 +/-2.2 hours/night and results were not stratified by compliance in the 15 patients who completed the study. Naegele et al re-examined 17 patients and 17 controls after 4-6mths of treatment and patients were found to have normalised most of their cognitive executive and learning disabilities, but all the short term memory tests remained unchanged (66). They did not find any difference in terms of neuropsychological results between compliant and non-compliant patients. There was no correlation between hours of nightly CPAP use (built in time counters) and daytime performance.

There is also evidence that even subjects with mild OSA show neuropsychological improvement following CPAP treatment. Engleman et al (67) showed improvement in mental flexibility after treatment for 1 month in 16 patients with mild OSA (AHI 5-14.9), but with no significant improvement in subjective or objective sleepiness. Kingshott et al attempted to identify predictors of improvement in daytime function in 62 subjects before and after CPAP and found that microarousal frequency and AHI were poor predictors of improvement in daytime function (68). Measures of hypoxaemia were better related but explained at most 22% of the variance.
Some of these treatment studies are now incorporating sham CPAP in a control arm. One such study in 46 subjects showed that neuropsychological function improved with therapeutic CPAP treatment but that these changes were not different to those occurring with placebo CPAP treatment, however this study may have been inadequately powered (69).

Population based studies

There is a wide inter-individual variability in daytime symptoms of OSA for the same polysomnographic severity. It is therefore important to see if the same pattern of neuropsychological deficit is seen in the general population as in clinically diagnosed OSA. Data from the Wisconsin Sleep Cohort Study, a population based study, show a significant negative association between log AHI and psychomotor efficiency score independent of age, gender and educational status. According to this data, an AHI of 15 (mild OSA) is equivalent to the decrement in psychomotor efficiency associated with 5 additional years of age (70).

In summary, the aetiology of neuropsychological deficits is probably multifactorial because there are weak and moderate correlations between the primary measure of severity of the disease (AHI) and quantitative outcomes, as well as partial reversibility with treatment. Attempts to correlate neuropsychological outcomes with a single sleep study parameter are artificial as measures of breathing disruption, hypoxaemia and sleep fragmentation are highly intercorrelated.

2.5 POSSIBLE MECHANISMS OF NEUROPSYCHOLOGICAL DEFICIT IN OSA

2.5.1 Sleep fragmentation

Studies of sleep fragmentation in which normal subjects were aroused by auditory stimuli regularly throughout the night show deficits in cognitive performance, specifically in attention based tests, and reduced rates of well-being. These changes are reversible (71).

2.5.2 Ischaemia and cell death

The detection of the presence or absence of structural lesions on brain imaging in OSA depends on the precise imaging modality used. Conventional magnetic resonance imaging in OSA shows no more ischaemic lesions than age matched controls. A case control study of magnetic resonance imaging (MRI) in 45 subjects with moderate to severe OSA and 45 controls matched for age, body mass index (BMI), alcohol and cigarette consumption, and treated hypertension showed a similar prevalence of sub-clinical cerebrovascular disease in the two groups (72). Hippocampal atrophy was seen in 25 patients with severe OSA and abnormal neuropsychological function, diagnosing atrophy by brain volumetric measures using quantitative MRI compared to a normative database (73). A further study of brain morphology by Macey et al using MRI showed diminished regional and often unilateral gray matter loss in sites including frontal and parietal cortex, temporal lobe, anterior cingulated, hippocampus and cerebellum in 21 patients with OSA compared to 21 controls (74). The finding of reduced grey matter concentration in the hippocampus has been replicated by another group (75). These results were not however replicated in a more recent study by O'Donoghue et al using two quantitative MRI techniques (an optimized voxel based morphometry technique and manual tracing of anatomical borders) where no gray matter deficits nor focal structural changes were seen in 27 subjects with severe sleep apnoea (76). Similarly no longitudinal changes were seen in gray matter density or regional volumes with 6 months CPAP treatment. The authors explain the discrepancy between their results and

those of Macey et al because the latter group did not statistically correct for multiple comparisons.

2.5.3 Changes in cell metabolism caused by ischaemia

It is known that in mild to moderate hypoxia, cerebral levels of ATP and adenylate energy charge are normal. Two studies have recorded no change in the cerebral metabolic rate for oxygen in human volunteers with a PaO2 of 35-40mmHg (quoted in (77)). OSA differs from chronic hypoxia as recurrent short desaturations may not trigger the same compensatory mechanisms. Metabolic changes suggestive of cerebral white matter damage have been found in one series of 12 patients with moderate to severe OSA, using magnetic resonance spectroscopy (78). Further work on 55 subjects by the same group showed a significant relation between AHI and the degree of metabolic impairment in cerebral white matter (79). All these subjects had normal MRI imaging. They also carried out magnetic resonance spectroscopy (MRS) examinations during sleep and demonstrated lactate production, suggesting that hypoxia may cause anaerobic glycolysis in the brain of subjects with moderate to severe OSA (80).

2.5.4 Animal model of chronic episodic hypoxia

Rats exposed to chronic episodic hypoxia demonstrated marked increases in apoptosis in one of the hippocampal regions (CA1) and in the cortex which decreased towards normoxic levels by 14 days and were accompanied by marked architectural disorganization in these brain regions and impaired performance during acquisition of a cognitive spatial task, without affecting sensorimotor function (81). This model enables the effects of episodic hypoxia to be assessed in the absence of significant sleep fragmentation (the rats' sleep patterns became normal after the first day). It also provides support to the volumetric MRI studies cited above showing hippocampal changes in subjects with OSA.

2.5.5 Neurotransmitters

Alteration of the cerebral redox state (reduction oxidation balance) in moderate hypoxia may cause alterations in neurotransmitter metabolism (47). Oxygen is utilised directly for the synthesis and degradation of dopamine, noradrenaline and serotonin. The Km (substrate concentration at which the enzyme is 50% saturated) of the synthetic enzymes

for O2 is 12μM whereas brain levels of oxygen are estimated to be between 2 and 25μM and so variations in oxygen concentration in the physiological range may affect enzyme activity. There is also a tight linkage between the oxidation of glucose and pyruvate and the synthesis of acetyl choline. Induction of chemical hypoxia in mice reduced acetylcholine synthesis as did "hypoxic" hypoxia at an arterial PaO2 of 60mmHg. Therefore hypoxia may mediate its effect via neurotransmitter metabolism.

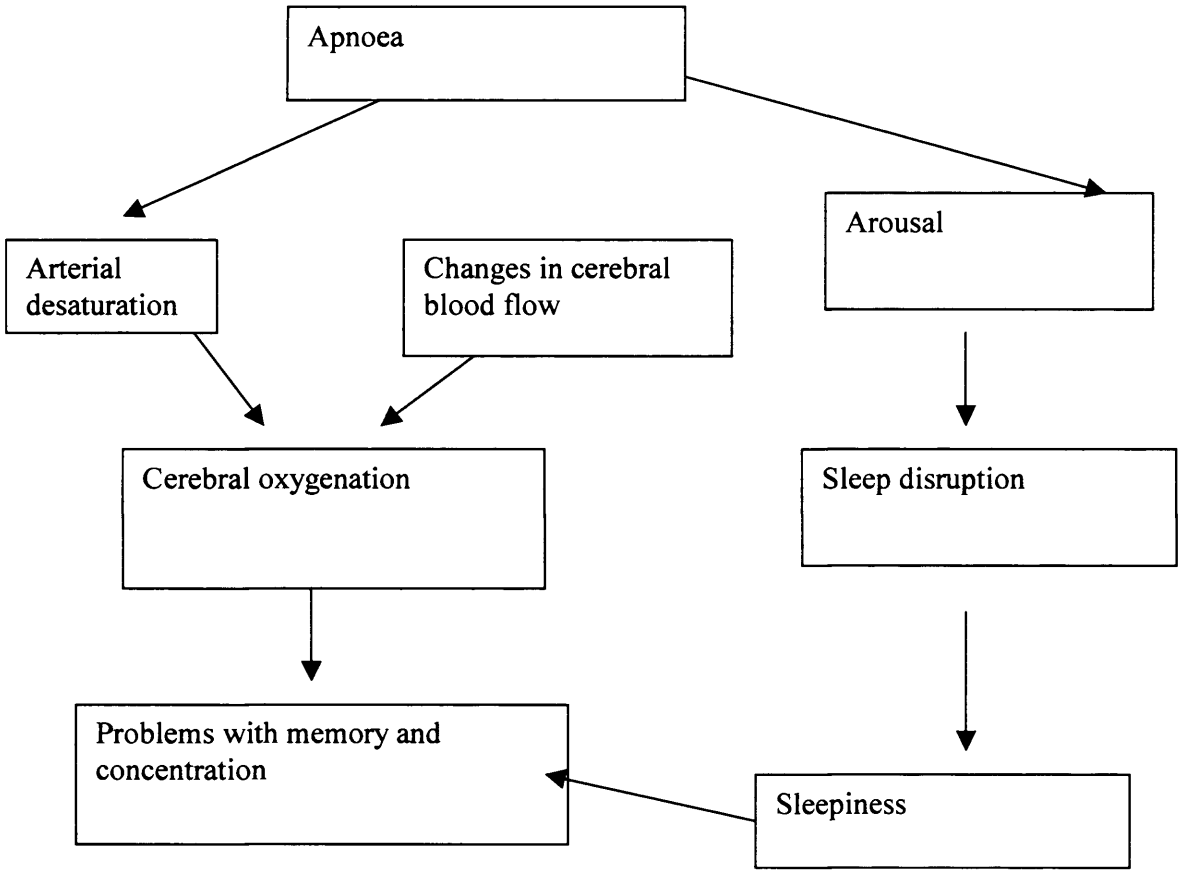
2.5.6 Hypertension and cerebrovascular disease

It is possible that the neuropsychological impairment in OSA is caused by subclinical cerebral vascular infarcts because of the increased risk of cerebrovascular disease. As discussed previously this increased risk is partly due to an increase in known risk factors: hypertension (39, 40, 42), and the metabolic syndrome (53, 56), but OSA also appears to be an independent risk factor for stroke (50, 52). However a case control study using MRI showed evidence of cerebrovascular disease to a similar extent in OSA patients and matched controls (72), so it is difficult to attribute the observed neuropsychological deficit to subclinical multi-infarct dementia on the basis of current evidence.

2.5.7 Summary

In summary there is evidence that both sleep fragmentation and hypoxaemia contribute to neuropsychological symptoms and objective deficit in OSA. Anatomical studies show both alterations in brain structure especially in the hippocampus, and metabolic changes in the brains of subjects with OSA. Few studies have combined objective neuropsychological testing with measures of cerebral physiology. We postulated that cerebral oxygenation measured directly may predict neuropsychological dysfunction better than measures based on pulse oximetry alone, as pulse oximetry will not measure changes in cerebral blood flow occurring during apnoea (see figure 2).

Figure 2. Outline of how obstructive sleep apnoea may cause daytime neuropsychological symptoms



2.6 THE USE OF NEAR INFRA-RED SPECTROSCOPY IN OSA

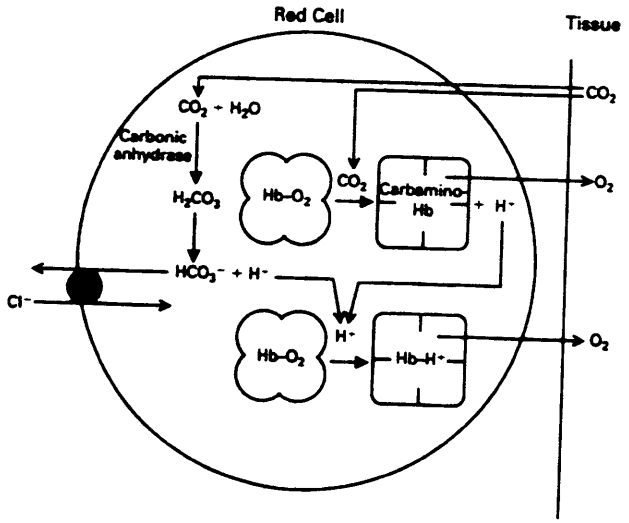
Near infra-red spectroscopy is a method of measuring cerebral oxygenation non-invasively and continuously, so that it is appropriate for use in overnight sleep studies. The theory behind the technique and its development and validation will be described in chapter 4. In brief, it is a spectroscopic technique based on the facts that body tissue is relatively transparent in the near infra-red spectrum, and that certain substances absorb light differently in the oxidized and reduced forms. The two substances imaged (chromophores) are haemoglobin and cytochrome oxidase.

2.6.1 Chromophores

Haemoglobin

Haemoglobin is a protein found in red blood cells which binds oxygen in the lungs and releases it in the tissues. Figure 3 shows the reactions involving haemoglobin which take place in the tissue capillary bed where oxygenated haemoglobin is reduced to the deoxygenated form. Arterial and venous blood are different colours because the absorption spectra of oxidized and reduced haemoglobin are different. The measurement of tissue haemoglobin concentrations gives an idea of the oxidation state in the tissues, and in addition total haemoglobin can be used as a proxy for blood volume. Some spectrophotometers also provide a tissue saturation measurement from the ratio of oxygenated to total haemoglobin.

Figure 3. Reactions involving haemoglobin in the tissue capillary bed (82)
This diagram illustrates how haemoglobin gives up oxygen and takes up carbon dioxide to become deoxyhaemoglobin.

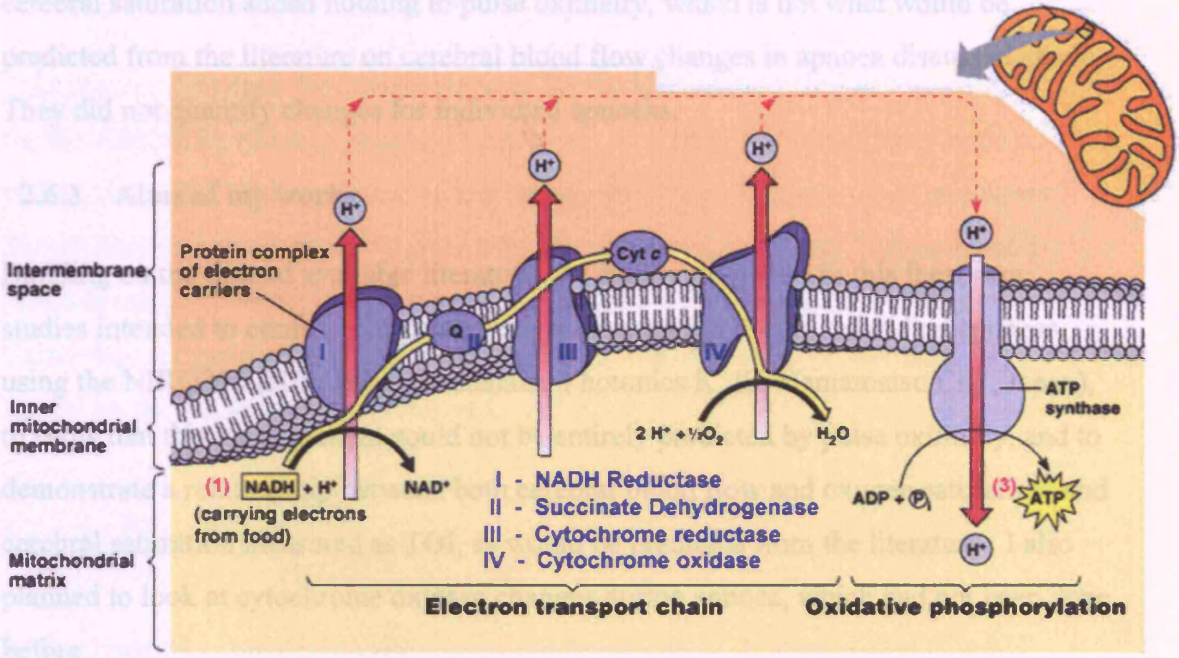


Cytochrome oxidase

Cytochrome oxidase is a mitochondrial enzyme which takes part in oxidative phosphorylation, ie it is responsible for the metabolism of organic intermediates using oxygen to make adenosine triphosphate. Figure 4 illustrates the mitochondrial metabolic pathways of the electron transport chain and oxidative phosphorylation,

where a series of enzymes in the inner mitochondrial membrane pump out protons against a concentration gradient and the resultant proton motive force drives ATP formation by another set of membrane enzymes.

Figure 4. The mitochondrial electron transport chain and oxidative phosphorylation
This shows the position of cytochrome oxidase on the inner mitochondrial membrane



2.6.2 Previous use of NIRS in OSA

Hayakawa et al (83) studied 8 men with moderate to severe OSA (mean apnoea index 35.7) using NIRS (OM-100A, Shimadsu) during nocturnal sleep (n=5) or daytime naps (n=3). They analysed 20 obstructive apnoeas during each of non-REM and REM sleep for each subject. They observed a consistent decrease of OHb and increases in HHb and total haemoglobin during each apnoea. Total haemoglobin change is obtained from the sum of OHb and HHb, and can be used as a measure of cerebral blood volume. An increase in cerebral blood volume is likely to be due to an increase in cerebral blood flow, unless venous return decreases. They interpreted their finding of a decrease in OHb despite an increase in total haemoglobin as suggesting that the increased cerebral blood flow during apnoea does not fully compensate for arterial desaturation and therefore a reduction in cerebral oxygenation occurs during apnoea.

The machine used in this study did not have the facility to measure cerebral saturation. Hausser-Haw et al measured cerebral oxygenation in 4 subjects with severe sleep apnoea (AHI 68-125/hr) and 4 snorers using a different NIRS machine, the Criticon 2020 (Johnson and Johnson Medical, England), (84). They reported that cerebral saturation paralleled peripheral oxygen saturation but was 20-30% lower in value in both snorers and subjects with OSA . These findings suggest that measurement of cerebral saturation added nothing to pulse oximetry, which is not what would be predicted from the literature on cerebral blood flow changes in apnoea discussed above. They did not quantify changes for individual apnoeas.

2.6.3 Aims of my work

Building on the limited available literature, the studies described in this thesis are studies intended to confirm changes in cerebral saturation during individual apnoeas using the NIRO300 (NIRO300, Hamamatsu Photonics K. K., Hamamatsu City, Japan), to show that this measurement could not be entirely predicted by pulse oximetry, and to demonstrate a relationship between both cerebral blood flow and oxygen saturation; and cerebral saturation measured as TOI, as would be predicted from the literature. I also planned to look at cytochrome oxidase changes during apnoea, which had not been done before.

Provided that these preliminary studies were satisfactory, I planned to go on to a large prospective clinical study to see if NIRS cerebral oxygenation measurements were clinically useful in predicting objective neuropsychological function in newly diagnosed subjects with OSA. In order to compare subjects I had to design ways of summarizing overnight NIRS recordings in a way similar to oxygen desaturation dip rates or T90 (time spent with SaO_2 <90%). Chapter 5 describes the methods used for data and statistical analysis. Chapters 6 to 11 describe the protocols and results of the validation studies and the protocol and measurements of the prospective study into cerebral oxygenation as a predictor of cognitive function in OSA. Chapters 12 and 13 describe pilot work on chronic hypoxia in COPD. All results are discussed in chapter 14.

3. BASIC METHODS

This chapter describes the equipment used for the studies described in this thesis, except for the NIRO300, which is described in Chapter 4. The polysomnography system, visilab, and NIRO300 machines were from the Middlesex Hospital sleep laboratory. Middle cerebral Doppler probe, laser Doppler cutaneous probe and Finapres blood pressure monitor were loaned from the Department of Neurosurgery, University of Cambridge, as part of the collaboration in the validation studies. Capnosleep® was loaned by the manufacturer Weinmann.

3.1 POLYSOMNOGRAPHY

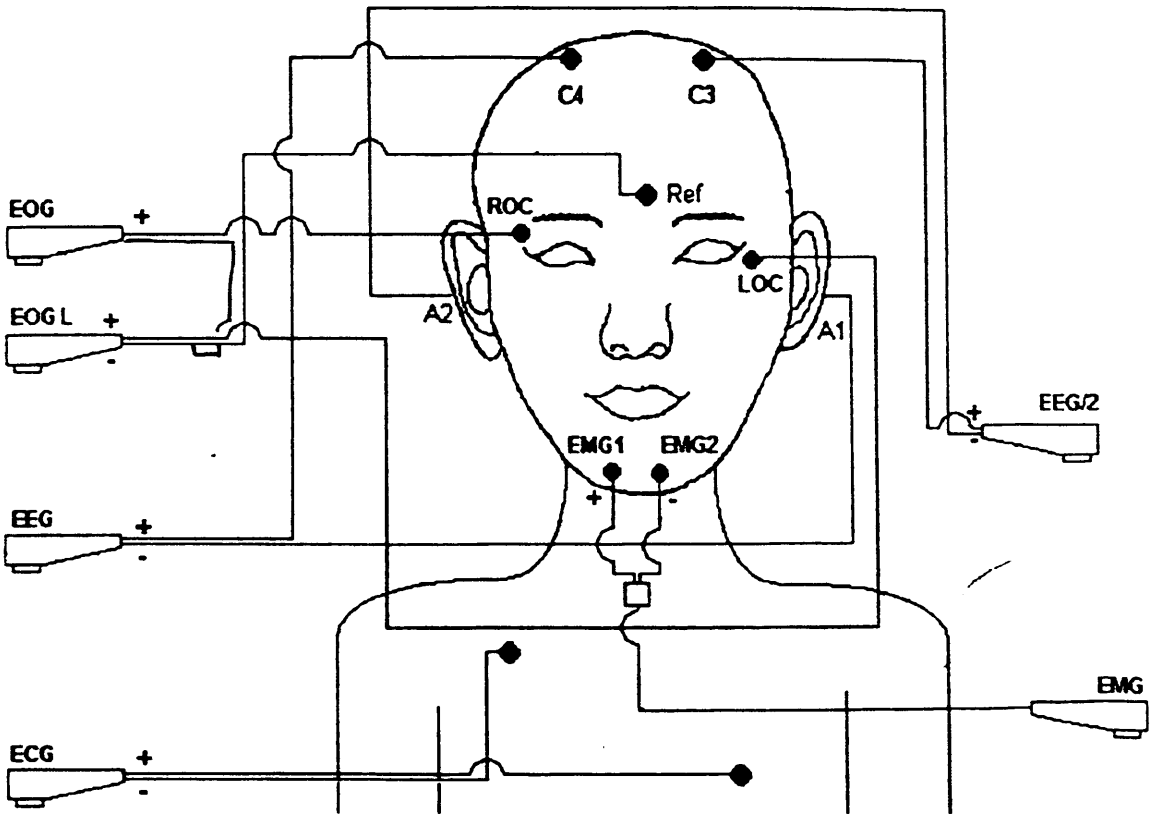
Full polysomnography is the classical neurophysiological technique used to study nocturnal sleep. It comprises measurement of EEG (C3/A2, C4/A1,) EMG, EOG, airflow, body plethysmograph, leg movements, body position, and oxygen saturation from a pulse oximeter. EEG, EOG and EMG are used to allow definition of sleep onset and sleep staging. Apnoeas and hypopnoeas are defined using saturation and airflow changes, with thoracic and abdominal movements allowing differentiation between obstructive and central apnoeas as well as being used in some definitions of hypopnoea. Body position is relevant as some subjects obstruct only when supine. Leg movements help to rule out alternative diagnoses.

The polysomnography system used in these studies was made by Compumedics® (S Series Sleep System, Compumedics, Melbourne, Australia). A heat sensitive thermistor was used to assess oro-nasal flow. Thoracic and abdominal respitrace bands were used to monitor chest and abdominal wall movements. The pulse oximeter was a Pulseox 7, (Pulseox 7, Minolta, now Anandic Medical Systems, Diessenhofen, Switzerland), which gives an analogue output every second to the polysomnography computer. The sampling rate should be set according to the rate of variation of the analogue signal.

There is a theorem in signal theory which states that the sampling rate must be at least twice the highest frequency in the waveform. The highest frequency of apnoeas is around a hundred per hour or once every 36 seconds. Although fine changes in saturation will be smoothed by this sampling frequency, it should pick up all apnoeas reliably. The pulse oximeter sampling frequency was identical to the TOI sampling frequency to which it was being compared. Electrodes were applied to the scalp using collodion glue prior to the sleep study in the positions as shown in the diagram (Figure 5).

Figure 5. Electrode positions for polysomnography

Electrodes are applied using collodion glue at the sites shown. EOG, EOGL, Ref – electro-oculogram positions; C4/A1, C3/A2 – EEG positions; EMG 1and 2 – EMG positions.



Sleep staging was performed manually according to standard criteria, see Table 2 (9).

Table 2. R & K sleep staging criteria

Sleep onset	3 or more continuous epochs of any stage of sleep
Stage 1 sleep	Mixed voltage mixed frequency, possible rolling eyes, in the absence of spindles, K-complexes or other identifying markers of other sleep stages
Stage 2 sleep	Spindles or k-complexes on a background of mixed voltage and frequency. Three minute rule adhered to.
Stage 3 sleep	20-50% of the epoch is comprised of delta waves (75μV amplitude) or larger.
Stage 4 sleep	50% or more of the epoch is comprised of delta waves or larger
REM sleep	Low voltage, mixed frequency EEG waves with rapid eye movements and a decrease in chin EMG. Three minute rule adhered to.

The three minute rule states that if there are no eg spindles or k complexes for up to three minutes, but there are some on epochs before and after, with no identifying markers of any other stage of sleep, then all of these epochs are scored as stage eg 2. An arousal was classed as 3 or more seconds of a significant change in the EEG. An arousal in REM sleep requires in addition an increase in chin EMG.
Obstructive apnoeas were defined as the cessation of airflow for more than 10 seconds in the presence of paradoxical movements of the rib cage and abdomen, accompanied by either a 1% desaturation or an arousal (85). Hypopnoeas were defined as a greater than 50 % reduction in thoraco-abdominal movement or airflow for at least 10 seconds accompanied by either a drop in oxygen saturation of at least 4 % or an arousal (86). The total number of respiratory events was divided by total sleep time to give an apnoea-hypopnoea index (AHI). Once manual staging has been completed, respiratory analysis is performed by the Compumedics® software to give an AHI and arousal index. The respiratory analysis can then be manually checked. When the cursor is clicked on a particular apnoea labeled on the airflow trace, a text box appears with the duration of the apnoea, sleep stage, saturation dip and minimum saturation within it.

Figures 6 and 7 illustrate a subject connected to full polysomnography and the computer readout.

Figure 6. Subject connected to full polysomnography (with NIRO300) at the Middlesex hospital

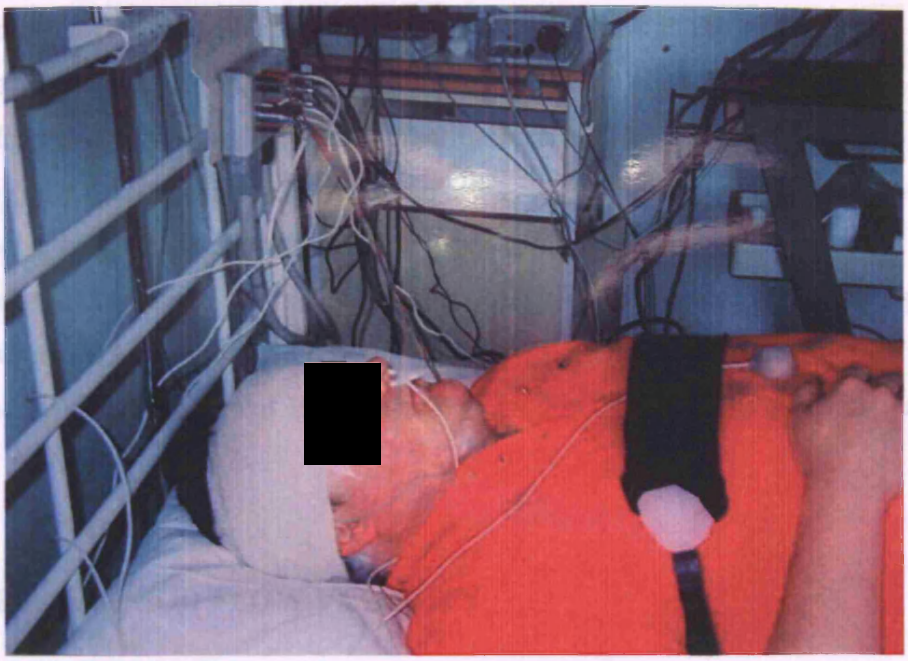
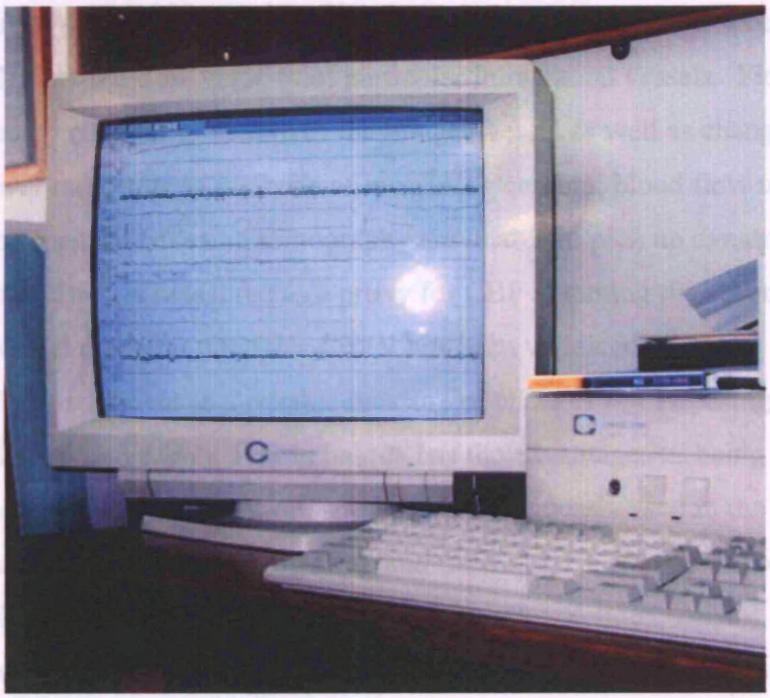


Figure 7. The polysomnography computer at the Middlesex Hospital



3.2 VISILAB SLEEP STUDY

This was the routine screening sleep study used to diagnose OSA in the Middlesex Hospital sleep clinic.

The Visilab sleep study (Visilab, Stowood Scientific Instruments, Oxford, UK) is a hospital sleep study system which consists of an infra-red video, microphone for snoring and pulse oximeter for heart rate and oxygen saturation. Body movement is calculated from the video and the system also calculates a 4% oxygen desaturation dip rate. Diagnosis of OSA is based on a dip rate of >10 with observation of obstructive apnoeas on the video. A dip rate of 10-30 constitutes mild OSA, 30-50 is moderate and >50 severe.

3.3 CEREBRAL BLOOD FLOW VELOCITY

Transcranial Doppler ultrasound can be used to measure middle cerebral artery cerebral blood flow velocity. Low frequency pulsed ultrasound waves penetrate the skull and the frequency shift of the waves reflected back from moving red cells at a specific depth can be used to calculate the flow velocity of particular intracranial vessels. Flow velocity is affected by changes in calibre of the imaged vessel as well as changes in blood flow, however radioisotope methods of measuring cerebral blood flow using xenon clearance or positron emission tomography are unable to pick up dynamic changes in CBF, so CBFV is measured as a proxy for CBF assuming the absence of changes in large vessel diameter. Doppler CBFV has been validated against radioisotope CBF measurement as a reliable measure of changes in CBF using blood flow response to hypercapnia (87). The technique has the advantages of being non-invasive and having rapid time resolution, and has been frequently used in the past for studies of haemodynamic changes during sleep and OSA (18-23, 27, 88). In our validation study the probe used was PCDop 842 (PCDop842, Scimed, Bristol, UK) positioned by an experienced user over the middle cerebral artery, and held in place by a custom-made head-band.

3.4 SCALP BLOOD FLOW

Measurement of scalp blood flow in the region of the NIR probes using laser Doppler flowmetry (LDF) allows observed changes in TOI to be related to changes in both intracranial and extracranial circulations, to confirm that the signal predominantly originates from the brain rather than from more superficial tissues. LDF samples from the local microcirculation to a depth of about 1-2mm, but this is probably representative of the extracranial block of tissue, as all are supplied from the external carotid artery. LDF does not provide an absolute value of skin blood flow and the readings are in arbitrary units, but provides a reliable measure of relative change. Most LDF devices use light at a wavelength that overlaps with the NIRS wavelengths, but the machine used in this study was specially modified to operate within the visible spectrum.
The instrument used was the MBF3D monitor and modified P3 probe (Moor Instrument Ltd, Axminster, Devon, UK) with the probe placed in the immediate vicinity of the NIR optodes (See Figure 8).

Figure 8. Positioning of carotid Doppler (black flex), and laser Doppler (white flex) probes. The NIRO probe is deep to the bandage

3.5 ARTERIAL BLOOD PRESSURE MONITORING

Continuous blood pressure monitoring was performed using a Finapres (Ohmeda 2300, Boulder, Colorado, USA) device on the index finger. This is a non-invasive machine to measure beat-to-beat blood pressure. The device utilizes a rapidly responsive servo-controlled balloon cuff, matched to the pressure within the finger arteries to measure arterial blood pressure. It is accurate for short periods, but is subject to drift over time and is too uncomfortable for prolonged studies. Invasive blood pressure monitoring was not thought to be justified in subjects with OSA.

3.6 CARBON DIOXIDE MONITORING

As partial pressure of carbon dioxide is one of the parameters which may affect the internal carotid circulation independently of the external carotid it was thought to be desirable to monitor pCO_2 by some means during the second validation study. Both non-invasive methods (endtidal CO_2 and transcutaneous CO_2) as well as arterial monitoring using paratrend were considered. One study has shown that neither non-invasive measure is consistently accurate when compared to arterial samples in sleeping patients (89). Paratrend is an invasive continuous intra-arterial monitor of pCO_2, pO2 and pH, which has not previously been used in OSA. It is accurate compared to arterial samples (90). We decided not to use it because of its cost (the probes are single use) and because we did not feel that its invasive nature was justified in our study population. We had access to a transcutaneous CO_2 monitor using a silver electrode (TINA TCM3 capnograph, Radiometer®, Copenhagen, Denmark) but the response time of 50s for 90% response meant that it was not suitable for resolving rapid changes during individual apnoeas. A transcutaneous system has been used previously in studies of cerebral haemodynamics during OSA (18, 30) but quantitative comparisons with CBFV were not made. We elected to use an endtidal CO_2 monitor (Capnosleep, Weinmann,Germany) which was designed for use in a sleep laboratory and has been validated against a thermistor as an apnoea marker in 121 subjects (91). It utilizes nasal cannulae which are much better tolerated during sleep than a tight fitting face mask, but have the disadvantages that they may entrain room air, and are inaccurate if the subject is mouth breathing (92). Apnoeas are defined by flattening of the $etCO_2$ trace to zero, so arterial pCO_2 during apnoea cannot be monitored using this technique, and maximum values before and after the apnoea are probably the most relevant readings. The increased dead space also complicates interpretation when nasal cannulae are used, especially in intermittently apnoeic patients. $EtCO_2$ monitoring has been used previously in studies of haemodynamics during OSA. $PetCO_2$ was found to be generally high in OSA patients compared to controls (19) and in one study a quantitative relationship between $PetCO_2$ and CBFV was observed (20).

4. TECHNIQUE OF NEAR INFRA-RED SPECTROSCOPY

Near infra-red spectrometry (NIRS) measures cerebral oxygenation non-invasively, based on absorption changes in chromophores which absorb in the NIR spectrum where body tissue is relatively transparent. NIR light from laser diodes is carried to tissue via optical fibres. Transmitted light is detected by a photomultiplier tube or photodiodes. The optodes, held in a small plastic holder, are attached to the forehead with a self-adhesive pad. Using incident and transmitted light intensities and knowing the specific extinction coefficients of the chromophores and the total optical pathlength, changes in concentration of the chromophores oxygenated and deoxygenated haemoglobin and cytochrome oxidase can be calculated (93). The technique enables concentration changes to be measured rather than absolute concentrations, some models eg the NIRO300 (NIRO300, Hamamatsu Photonics K.K., Hamamatsu City, Japan) also measure a regional tissue saturation, tissue oxygenation index (TOI), by spatially resolved spectroscopy (94)

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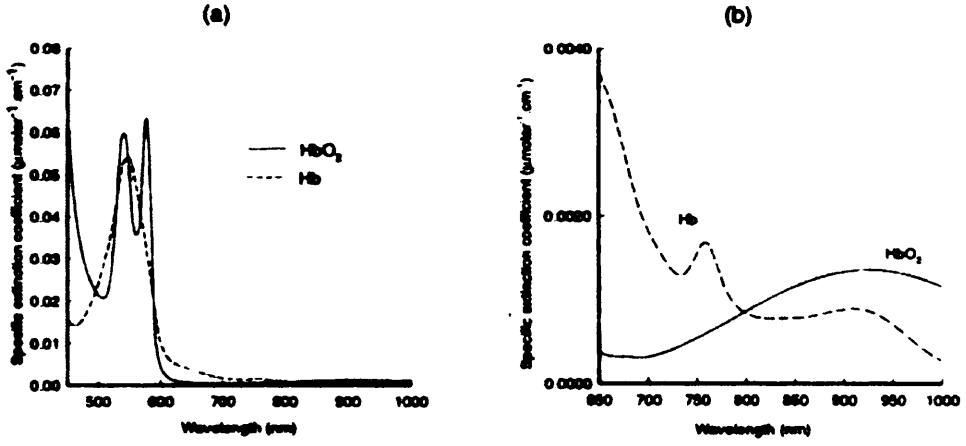
4.1 INITIAL DESCRIPTION AND THEORY OF THE TECHNIQUE

The use of light in the near infrared spectrum to image tissue oxygenation was first described by Jobsis (95). Visible light (wavelength 450-700nm) is strongly attenuated by tissue and penetrates to a depth of less than 1cm. Light in the near infrared spectrum (wavelength 700 – 1000nm) penetrates to a greater depth, and can be detected at 8cm. Hence it can be used to image concentration changes of substances whose absorption

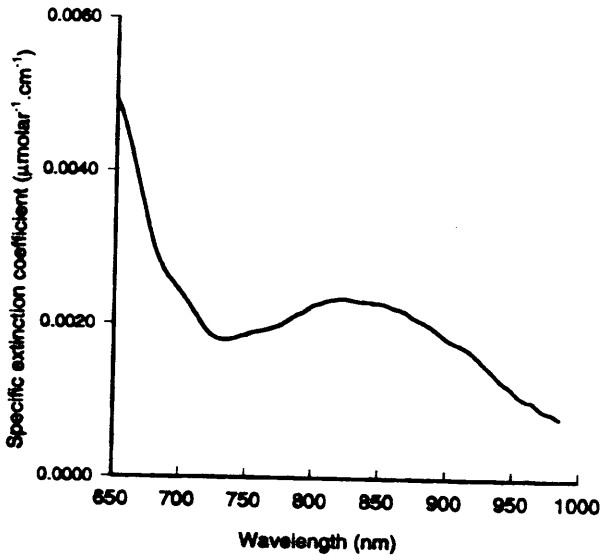
varies at these wavelengths according to oxidation state. Important compounds which can be imaged are oxyhaemoglobin (OHb), deoxyhaemoglobin (HHb) and cytochrome oxidase (Cytox). Other biological compounds also absorb light (eg water, bilirubin, melanin) but their concentration is unlikely to change during the measurement period. For an absorbing compound dissolved in a non-absorbing medium, measured attenuation can be converted into concentration using the Beer Lambert Law which states that the attenuation is proportional to the concentration of the compound, the specific extinction coefficient of the compound and the optical pathlength. Adaptation of this law to deal with an absorbing compound in human tissue is necessary and is described below. The specific extinction coefficient of the compound varies with wavelength. The absorption spectra for oxy and deoxy haemoglobin in the NIR spectrum are illustrated in Figure 9.

Figure 9. Absorption spectra for oxy and deoxy haemoglobin in the range (a) 450-1000nm and (b) in the near infrared region 650-1000nm (93)



We know that oxygenated and deoxygenated blood can be visually distinguished – this difference in absorption spectra persists in the NIR region and allows spectroscopic separation of the compounds using only a few wavelengths. The other compound which is measured using NIRS is cytochrome oxidase and the difference absorption spectrum between the oxidized and reduced forms is illustrated in Figure 10 (as the absolute concentration does not change knowledge of the individual absorption spectra of the oxidized and reduced forms is not required).

Figure 10. The difference absorption spectrum between the oxidized and reduced forms of cytochrome oxidase (93)



Cytochrome oxidase is the terminal enzyme in the mitochondrial respiratory chain, and so changes in its oxidation state may reflect changes in the status of oxidative phosphorylation in the cell. However the enzyme has several redox centers, only one of which is imaged by NIRS, and this complicates interpretation. Although the magnitude of the specific absorption coefficients is similar to those of haemoglobin, the concentration in tissue is much less, and so separation of the absorption changes due to cytochrome from the haemoglobin changes is difficult. Validation of NIRS measurement of cytochrome oxidase will be discussed later.

As well as being absorbed in the tissue, light is also scattered within the tissue and so the distance it travels (pathlength) is not just the linear distance between emitter and detecter. Scattering occurs as light passes across boundaries between substances of different refractive indices. Both cell membranes and the macroscopic boundaries between different histological structures (bone, blood vessel, white matter) cause scattering. A differential pathlength factor (DPF) is therefore introduced into the Beer Lambert Law as a multiplier of the geometric pathlength to correct for tissue scattering. An unquantifiable amount of light is lost due to scattering, and so the modified Beer Lambert Law only allows calculation of changes in chromophore concentration, with

the assumption that the scattering loss remains constant for the same individual during the recording period. There are several methods that have been used to calculate DPF for different tissues. The time an optical pulse takes to pass through tissue has been measured by splitting a pulse of light produced by a laser beam so that part of the output goes directly to a streak camera and the rest passes through the tissue first. This is known as the time of flight method and can only be carried out in an optical laboratory so cannot be used clinically. A second method uses an intensity modulated optical spectrometer to measure total pathlength from the phase shift occurring between light entering and exiting the tissue. This enables continuous real time measurement of total path length and is particularly necessary when there are changes in geometric pathlength during the study, for example when studying the fetus during labour or exercising muscle. Where geometric pathlength is fixed, the technique can be used to measure DPF. This technique has been used to measure DPF in neonatal head, and adult head, forearm and calf (96). The estimate of pathlength used in this thesis comes from a study of cranial DPF in 283 subjects, which showed a slight age dependence of DPF (97).

4.2 USE OF NIRS IN ADULTS

The earliest clinical use of NIRS was in neonates, where it was possible to transmit NIR light across the skull. This early work documented changes in NIR indices in response to alterations in arterial oxygen saturation, carbon dioxide tension and tilting (98, 99). In neonates, although the precise path length may be imprecisely known, the fact that the major part of the tissue sampled is brain is not in question. It is not possible to use transcranial illumination in adults because of the bigger distances involved and so reflectance spectroscopy (scattered light sampled by an ipsilateral receiving probe) is employed instead. Figures 11 and 12 illustrate transcranial and reflectance spectroscopy.

Figure 11. Example of basis NIRS circuit using transcranial illumination (IOS = intra –optode space) (93)

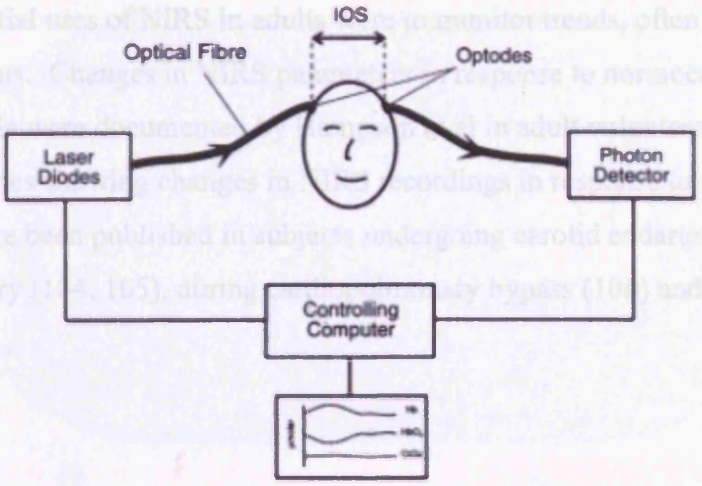
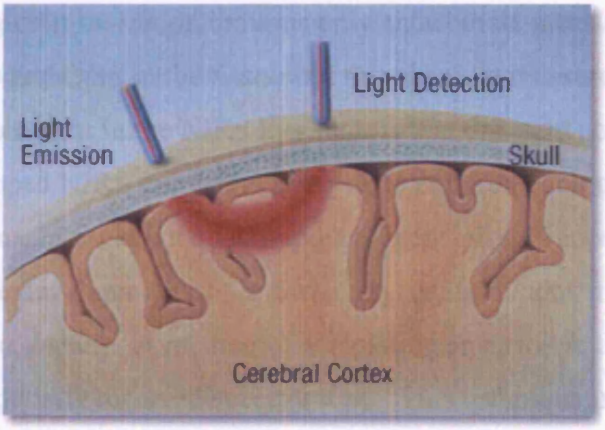


Figure 12. Illustration of the principle of reflectance spectroscopy as used in adult NIRS



The area imaged surrounds the interoptode dimension to a depth of a few cm. The penetration depth of NIR light depends on intraoptode spacing (100) and can be calculated using theoretical modelling to be 1.2 to 2cm at a spacing of 2.7cm (101). Penetration into the cerebral cortex has been confirmed using dye techniques (101). The standard left frontal probe position is chosen because of practical considerations (lack of overlying muscle, sinuses or hair). Haemoglobin imaged is therefore

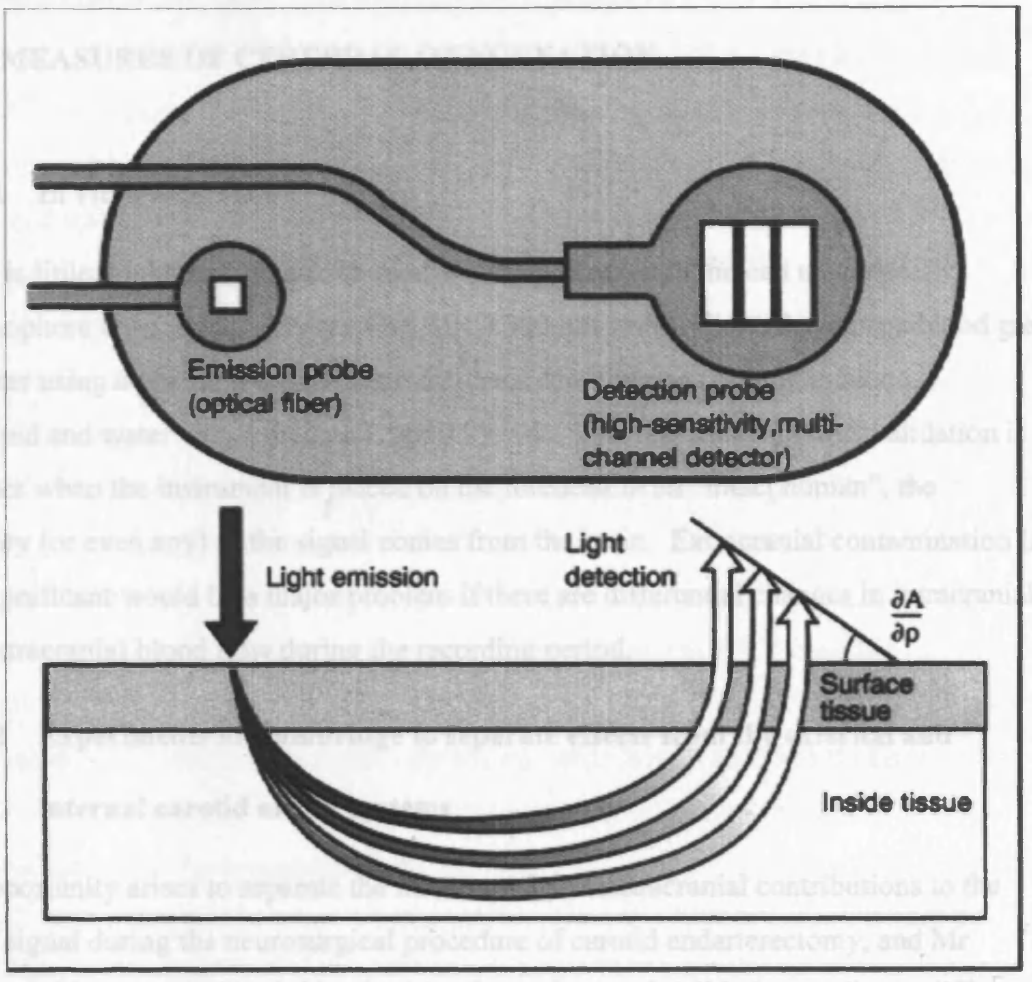
predominantly within the left frontal cortical microcirculation, consisting on average of 75% venous, and 25% arterial or capillary blood.

With the limitations of uncertain spatial resolution, and the inability to measure absolute concentrations, initial uses of NIRS in adults were to monitor trends, often in unconscious patients. Changes in NIRS parameters in response to normocapnic and hypocapnic hypoxia were documented by Hampson et al in adult volunteers (102). Observational studies showing changes in NIRS recordings in response to physiological insult in adults have been published in subjects undergoing carotid endarterectomy (103), in head injury (104, 105), during cardiopulmonary bypass (106) and during anaesthesia (107).

4.3 DEVELOPMENT OF THE TISSUE OXYGENATION INDEX OF THE NIRO300

As described above the NIRS machines used in early studies measured only changes in chromophore concentration from an arbitrary baseline. Absolute concentrations cannot be measured because of the complex light scattering in the tissue. Calculation of an absolute tissue haemoglobin saturation requires only an accurate measurement of the relative amounts of Hb and OHb in the tissue and this absolute measure is potentially easier to obtain. One problem in the NIRS literature is that different commercial companies have developed NIRS oximeters using different methodology and algorithms and validation of one machine cannot be extrapolated generally. Hence in this review I shall concentrate on the development of the tissue oxygenation index measure of the NIRO 300 (Hamamatsu, Japan). A method of calculating an absolute tissue saturation was developed using spatially resolved spectroscopy. This technique involves transmission of light at multiple wavelengths from a laser emitter and detection by multiple detectors at fixed distances from the emitter. The basic measurement made is the rate of increase of light attenuation with respect to the source detector spacing at different wavelengths, as illustrated in Figure 13.

Figure 13. Principle of spatially resolved spectroscopy in the NIRO300



Using assumptions from photon diffusion theory to calculate the scattering coefficient, these measurements are converted to relative absorption coefficients and then relative concentrations of OHb and HHb. TOI is given by the ratio of OHb to OHb + HHb. A prototype machine using this methodology was developed in 1993 (108), and it was incorporated into a commercial spectrometer, the NIRO 300 in 1999, (94). In the NIRO 300 light emitted at four wavelengths by a laser is scattered by the tissue and reflected light is detected by 3 closely spaced photodiodes. Conventional measurements of OHb, HHb and cytox without spatially resolved spectroscopy are also taken.

4.4 APPROACHES TO VALIDATION OF NIRS INSTRUMENTATION AS MEASURES OF CEREBRAL OXYGENATION

4.4.1 In vitro validation

There is little doubt that in uniform media NIRS instrumentation can measure chromophore changes accurately. The NIRO 300 has been validated against a blood gas analyzer using a phantom containing 6 different combinations of human blood, intralipid and water with a median R^2 of 0.99 (94). The real issue in NIRS validation is whether when the instrument is placed on the forehead in an "intact human", the majority (or even any) of the signal comes from the brain. Extracranial contamination if it is significant would be a major problem if there are differential changes in intracranial and extracranial blood flow during the recording period.

4.4.2 Experiments in Cambridge to separate effects from the external and internal carotid artery systems

An opportunity arises to separate the intracranial and extracranial contributions to the NIRS signal during the neurosurgical procedure of carotid endarterectomy, and Mr Kirkpatrick's group in Cambridge have performed several validation studies in different NIRO machines using a formalized protocol and multiple monitoring modalities during the procedures. Their initial study using the NIRO1000 (Takamatsu) was on 13 subjects, 8 of whom showed a fall in MCA flow velocity on clamping the internal carotid artery. They showed a close relation between flow velocity changes and OHb, with no effect of clamping the external carotid on measured parameters (103). Subsequent studies were performed using the NIRO500, using a standardized protocol where the external carotid was clamped 2 minutes before the internal carotid in controlled intraoperative conditions where ABP, endtidal CO_2 and SaO_2 were kept constant. Continuous measurements of Doppler CBFV, cutaneous flow using a modified laser Doppler flowmeter, ABP, $etCO_2$, NIRO300 OHb and HHb , were made. This allowed monitoring of the intracranial cerebral circulation with TCD and monitoring of the extracranial circulation with the laser Doppler. The findings were that both the ECA and ICA vascular territories contribute to the NIRS changes during

carotid endarterectomy (109), and that once the ECA component was removed, NIRO values could be used to predict severe cerebral ischaemia by established criteria (110). The initial results with the NIRO 1000 may be explained by the fact that the early machine required tight bandaging of the optodes to the head which may have rendered local skin ischaemic. At this stage the conclusion was that NIRS was capable of measuring intracranial ischaemia but only if the extracranial component was specifically monitored and removed.

The same experimental setup was used to validate the NIRO300 TOI measurement obtained by spatially resolved spectroscopy. Using sequential clamping of internal and external carotids in 60 patients during carotid surgery, TOI changes were seen in 49 subjects; during external carotid clamping in 8, and during internal carotid clamping in 41. TOI correlated significantly with cerebral blood flow velocity ($r=0.56$) but not with cutaneous laser-Doppler flowmetry ($r=0.13$). Discounting the 8 subjects in whom clamping the external carotid affected systemic blood pressure and CBFV, the sensitivity of TOI to intracranial and extracranial changes was 87.5% and 0% respectively, and specificity was 100% and 0% respectively (111). This was the first time that an NIR machine was rigorously shown not to have a significant extracranial contribution, and suggests that the algorithms used for the spatially resolved spectroscopy select for intracranial signal.

4.4.3 Cerebral activation measurements

Further evidence in support of an intracranial source for NIRS signals comes from functional imaging studies where changes in brain activity are assessed in response to stimuli. Activation of part of the brain is accompanied by a local increase in blood flow. Characteristic NIRS signal changes have been observed in response to motor activity, visual activation, auditory stimulation and performance of cognitive tasks, all observed non-invasively in adult humans (reviewed in (112)). Optode positioning for monitoring of frontal cognitive function is similar to that recommended when the instrument is used as a cerebral oximeter. Cognitive stimulation by performing calculations resulted in reproducible increases in OHb and decreases in HHb (NIRO500), with no change in cutaneous blood flow monitored using LDF (113). Similar studies have not been performed using the NIRO300. The fact that cerebral activation can be detected by NIRS confirms the depth of penetration, but is one of the

reasons for the lack of reproducibility of the measurements. When the instrument is used as a cerebral oximeter the assumption is made that the local changes in cerebral oxygenation represent global changes occurring in response to a global hypoxaemic or haemodynamic challenge. Luckily most clinical uses of a cerebral oximeter are in subjects who are unconscious whether due to cerebral insult or anaesthesia, and this assumption probably holds true in these circumstances.

4.4.4 Jugular bulb saturations

Cerebral oxygenation is conventionally monitored by measuring the saturation of the venous effluent of the brain: jugular bulb saturation. When NIRS measurements are validated against jugular bulb saturations, correlation has not been good (114, 115). As the jugular bulb saturation gives a global measure and NIR is local, discrepancy between the values obtained may be real. When used as a tool to detect events causing change in cerebral perfusion pressure and MCA flow velocity in ventilated patients with head injury, NIRS (NIRO1000) showed correlated changes in 37 of 38 events, and jugular venous saturation monitoring only showed correlated changes in 20 (105). The spatially resolved spectrometer (SRS) (prototype for the NIRO 300) was assessed against jugular bulb oxygen saturation in 24 subjects undergoing routine cardiopulmonary bypass and showed good correlation in 12 of the 24 subjects (116). The range of changes seen with the SRS was not as great as with the jugular saturation measurements, and tended to be 10-15% lower than the jugular saturations. Hence the SRS was no better than earlier models when compared with jugular bulb saturations on cardiopulmonary bypass, however interpretation of this lack of correlation is complicated as one method measures local tissue saturation, the other global venous saturation, and the conditions of non-pulsatile blood flow and hypothermia during bypass may affect the cortical microcirculation.

A similar study using the NIRO300 was published after I had completed the pilot work described in this thesis. Seventeen subjects undergoing warm coronary artery bypass surgery were studied, measuring TOI and jugular bulb saturation (SjO2) at various timepoints during cardiopulmonary bypass. Again there was a bias (TOI – SjO2) of –6.7%, and wide limits of agreement between the two methods, suggesting that they are not interchangeable (117).

4.4.5 Tissue oxygenation measurements

So is there any currently used method of measuring cerebral oxygenation against which NIRS can be validated that is more appropriate than jugular bulb saturation? One method introduced in neurosurgical intensive care units in 1993 is monitoring of local oxygen pressure in brain white matter (tipO2). One group has compared this method with NIRS cerebral saturation (measured using the Invos 3100 NIRS machine (INVOS, Somanetics Corporation, Troy, Michigan, USA)) in 12 patients, 3 with subarachnoid haemorrhage and 9 with traumatic brain injury (118). Because they were comparing a pO2 with a saturation they used frequency based mathematical methods to compare the two methods and concluded that the two signals contain similar information, with a band of significantly correlated frequencies in more than 90% of the data sets for coherence and overall density distribution. Cerebral blood flow and oxygenation is also monitored using PET scanning, however PET has very good spatial resolution and poor time resolution, in comparison with NIRS which has excellent time resolution and poor resolution in space. PET has therefore been used in an attempt to refine the spatial resolution of NIRS and 2 studies using PET and NIRS simultaneously have shown the best correlation between the two techniques in the outer 1cm of the brain tissue.

4.4.6 Against other machines

As there is no "gold standard" measure of local cerebral oxygenation for NIRS validation, an alternative approach is to compare cerebral saturation measurements simultaneously from 2 different NIRS machines. Five studies have been carried out using the NIRO300, 4 comparing it to INVOS 4100 and 5100 (119-122), and one to the OM-200 (123). Clearly interpretation of the results would be easier if there were good correspondence between values, than if, as is found, correspondence is poor, as the latter could mean that either or both machines are invalid as absolute measures. These studies do not therefore help much towards validation. The INVOS systems use different assumptions and algorithms to calculate a tissue saturation, involving two wavelengths of light, an assumption of a fixed partition ratio of blood between arterial and venous compartments, and elimination of extracranial contamination by simple subtraction. One study compared NIRO 300 and INVOS 5100 in juvenile swine undergoing cardiac bypass surgery and showed an overall correlation of 0.82 between the two systems, but a correlation of baseline readings of 0.62, with a non-linear

relationship (120). Comparison of the same machines in paediatric surgical patients again showed poor agreement, with the INVOS measurements significantly higher (119). In adult volunteers the INVOS 5100 underread cerebral oxygenation compared to the NIRO300, with an overall bias of -0.1% and limits of agreement of 14.7% (121). Two of these studies commented that the two machines demonstrated similar changes in response to challenge (120, 121). A study of the INVOS 4100 and the NIRO 300 in 19 patients during CO_2 challenge showed a bias of –0.5% with 2 SD of 15.6% when comparing the INVOS regional saturation (rSO2) with the TOI value, and a bias of –3.4% with 2SD of 15.2% when comparing the percentage change of rSO2 with percentage change of TOI, indicating unacceptable disagreement (122). Comparison of NIRO300 with OM-200 in forearm muscle at rest and during arterial occlusion, showed a significant correlation at rest (r^2= 0.43, n=33) but not during arterial occlusion (123). Overall these studies suggest that the choice of algorithm and assumptions used for calculation of cerebral saturation from NIRS measurements does have an effect on the absolute values obtained, and so results obtained using different machines are not interchangeable.

4.4.7 Using clinical endpoints

Various attempts have been made to demonstrate clinical usefulness of NIRS machines to predict clinical outcomes in adults. The two main clinical situations where this has been attempted are carotid endarterectomy and cardiac surgery.

Nollert et al performed neuropsychological testing using the Mini-Mental-State test before and after cardiac surgery during which 41 subjects were monitored using NIRS (NIRO 500), (124). The 4 subjects who demonstrated a reversible neuropsychological deficit post operatively (score of 23 or below) had a bigger decrease in NIR measured oxidized cytochrome oxidase than the others. No other measured parameter was significantly associated with neuropsychological deficit. More recently Reents et al measured intraoperative regional cerebral oxygen saturation using NIRS (INVOS 4100) in 47 patients undergoing cardiopulmonary bypass for coronary artery surgery and found this not predictive for post operative cognitive performance measured using a five test battery (125). 16 patients in this study showed postoperative cognitive dysfunction and cytochrome oxidase results are not reported.

Kirkpatrick's group have attempted to define thresholds for critical ischaemia during carotid endarterectomy using NIRS (126). Severe cerebral ischaemia (SCI) was defined

as an intraoperative fall in Doppler measured MCA flow velocity of more than 60% accompanied by a sustained fall in cortical cerebral activity measured using a three-lead cerebral function monitor. The machine used did not have a cerebral saturation available and changes in OHb and HHb were resolved into external and internal carotid components using interrupted time series analysis following staggered clamping. The NIRS parameter chosen for comparison was the internal carotid (ICA) ΔHbdiff (ΔOHb-ΔHHb, which is a reasonable estimate of changes in oxygenation status independent of changes in blood volume). This value correlated with the percentage change in flow velocity (%ΔFV) (r=0.73). 16 subjects fulfilled the criteria for SCI and an ICA ΔHbdiff of 6.8μmol/l was 100% specific for SCI, whereas a value less than 5μmol/l was 100% sensitive for excluding SCI. Samra et al measured regional cerebral oxygen saturation (Invos 3100) in 94 subjects undergoing carotid endarterectomy and showed that the mean decrease in cerebral saturation was greater in 10 subjects who developed post operative neurological symptoms (change in mental state or contralateral motor deficit) than in the others (127). A 20% fall in cerebral saturation had a sensitivity of 80% and specificity of 82.2% as a predictor of neurological compromise.

4.4.8 Summary

In the absence of a technique for direct validation of the technique of NIRS for cerebral oximetry in humans, a number of different validation methods have been developed. These include separation of the intracranial and extra cranial circulations during carotid endarterectomy, cerebral activation measurement, validation against jugular bulb or tissue oxygenation measurements, validation against clinical endpoints and against other NIRS machines. Each of these techniques has some drawbacks, but each has added useful information about the usefulness of NIRS measurements in clinical situations. Validity in vitro is not in question.

4.5 VALIDATION OF THE NIRO300

The TOI measurement of the NIRO300 is an absolute tissue saturation measurement which has been validated as intracranial during carotid endarterectomy (111), as well as validated against a blood gas analyzer in vitro and against time resolved spectroscopy in human arm (94). The main limitations of the technique are poor spatial resolution, lack

of reproducibility and the possibility of extracranial contamination when the instrument is used in situations less controlled than operating theatres, ie when there are variations in blood pressure and oxygen saturation.

4.6 VALIDATION OF THE CYTOCHROME OXIDASE MEASUREMENT

The main theoretical problem in measurement of cytochrome oxidase using NIR is whether it is possible to resolve spectral changes due to cytochromes in the presence of much larger concentrations of haemoglobin. In animal models using inhalation of 100% nitric oxide and exsanguination the cytochrome oxidase algorithm has been shown to be robust to large changes in haemoglobin oxidation and concentration (128). When cytochrome oxidase was fully reduced with cyanide, it was not possible to create spurious signals by manipulating haemoglobin concentrations (129). Hence in experimental conditions it is currently thought that NIRS can accurately measure changes in the cerebral cytochrome oxidase redox state (129).

The possibility of extracranial contamination is less of an issue with cytochrome oxidase measurement than with haemoglobin measurement, as mitochondrial content of tissues varies with metabolic activity, and is higher in brain than bone or skin, and absent in red cells. Thus the signal is unlikely to be significantly contaminated by the extracranial blood flow changes that occur during apnoea. Theoretical modeling suggests that the area imaged is restricted to the cerebral grey matter beneath the optodes. Functional imaging of occipital cortex during visual stimulation confirms an intracranial source for the cytochrome oxidase signal (112).

NIR cytochrome oxidase signals have also been validated against magnetic resonance spectroscopy (MRS) as a predictor for cerebral energy loss in hypoxic piglets (130). Decreases in phosphocreatine and nucleoside triphosphate compounds correlated closely with decreased cytochrome oxidase, but not with haemoglobin changes. Another study using an animal model of cardiopulmonary bypass also showed correlation between cytochrome oxidase and high energy phosphates using MRS. Maximal cytochrome oxidase reduction during deep hypothermic respiratory arrest predicted histological brain damage (131).

4.7 THE TOTAL HAEMOGLOBIN MEASUREMENT

The sum of the OHb and HHb changes give a total haemoglobin change within the

imaged area, which is related to a change in cerebral blood volume. Cerebral blood volume change can be calculated from THb using corrections for cerebral large to small vessel haematocrit ratio, cerebral tissue density and subject haemoglobin concentration as previously described (93). Changes in THb show significant correlation with changes in Doppler cerebral blood flow velocity in adult cerebrovascular reactivity testing (132). Therefore in the absence of more extensive monitoring the THb measurement available from NIRS has been used to give information about haemodynamic changes in brain tissue (26, 83).

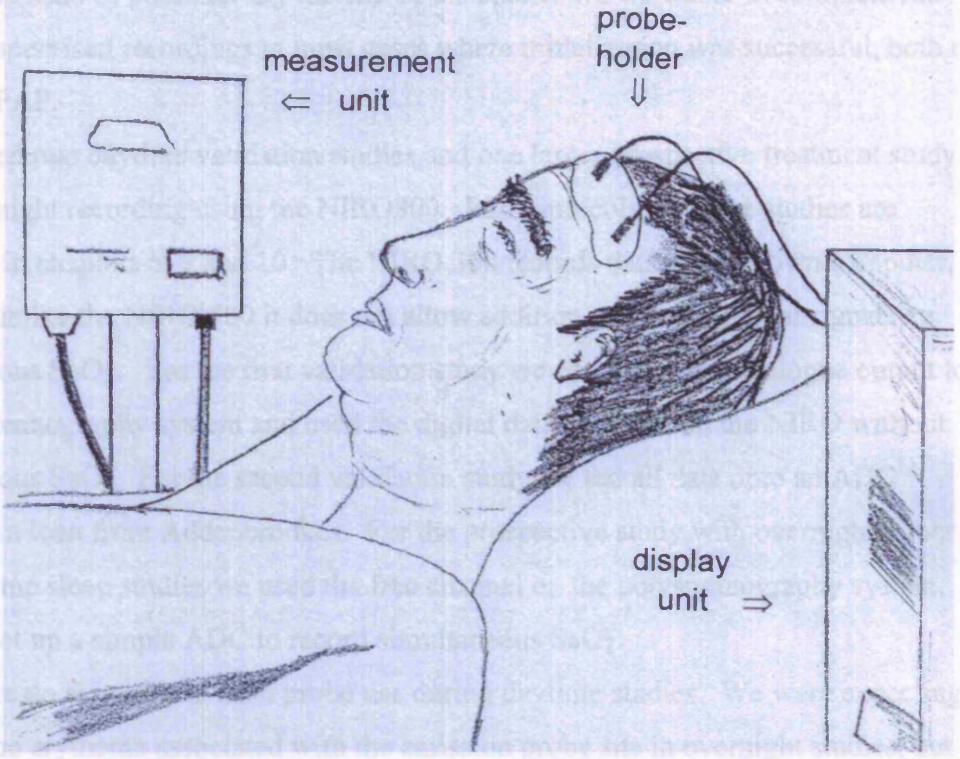
4.8 CLINICAL USE OF THE NIRO300

The NIRO 300 consists of a measurement unit and a display unit, as well as emitter and detector probes connected to the measurement unit by optic fibres. Figure 14 is a photograph of this instrument.

Figure 14. Photograph of the NIRO 300 (Hamamatsu Photonics K.K., Japan)

A laser light source within the measurement unit emits light in the near infra-red spectrum. First both probes are slotted into position at the end of the measurement unit so that a probe test may be carried out. Probe testing fails if the probe is dirty or if optic fibres are damaged. After a successful probe test the probes are inserted into the probe holder which holds them at a fixed distance of either 4 or 5 cm. In general 5 cm is preferred as theoretically the greater the interprobe distance the more accurate are the assumptions that the scalp between them is flat. The probe is positioned high and laterally on the forehead towards the temporal region, away from the frontal air sinuses, and avoiding hair (see Fig 15).

Figure 15. Probe positioning for the NIRO300



A double sided self-adhesive sticker is used to secure the probe either before or after initialization. Initialisation is then carried out where the laser selects an output to suit the attenuation characteristics of the particular position selected. Various error messages may be seen at this stage. Signal underflow may be overcome by repositioning the probes at a distance of 4cm. Signal overflow at 5cm may be overcome by the use of the attenuator supplied with the machine, effectively a little spacer that increases the distance between the emitter cable and the source. Pressure over the probe site may also alter initialization readings, and simple repositioning often helps. On initialization the figures shown on the screen give some idea of how hard the laser is having to work at the different wavelengths, and figures of 31, suggest underflow, where figures of less than 10 suggest overflow. Light shielding is rarely a problem in sleep studies unless the bedside lamp is pointing towards the head in which case the error message "improve light shielding" appears and can be improved by repositioning or switching off the light. Following successful initialization the recording can be started. Once recording was started we initially had problems with loss of contact/poor light shielding, but these improved when we became more aware of the importance of

keeping the room darkened and positioning the measurement unit on a drip stand as close to the head as possible. By the end of the studies we were able to complete full night unsupervised recordings in most cases where initialization was successful, both on and off CPAP.

I performed two daytime validation studies and one larger prospective treatment study with overnight recording using the NIRO300. Full protocols for these studies are described in chapters 6, 9 and 10. The NIRO 300 records data onto its own computer, however unlike the NIRO 500 it does not allow addition of any additional signals eg simultaneous SaO_2. For the first validation study we connected the analogue output to the polysomnography system and used the digital data recorded on the NIRO without simultaneous SaO_2. For the second validation study we fed all data onto an ADC analyzer on loan from Addenbrookes. For the prospective study with overnight rather than daytime sleep studies we used the free channel on the polysomnography system, and also set up a simple ADC to record simultaneous SaO_2.

There were no side effects from probe use during daytime studies. We were expecting to see some erythema associated with the emission probe site in overnight studies, but in fact only observed very occasional mild reactions. I have subsequently become aware that continuous NIRO monitoring, for example following head injury is taking place for several consecutive days on neurosurgical ITUs without ill effects. There is a theoretical risk of retinal injury from the laser source if it is switched on without the probe in position, but in practice this is impossible to do. Hence we showed NIRO300 to be a reasonably side-effect-free and easy-to-use addition to full polysomnography in subjects with obstructive sleep apnoea.

5. PRINCIPLES OF DATA ANALYSIS

The output from the NIRO 300 presented several problems for data analysis. Output consisted of measurements of concentration changes in oxidized cytochrome oxidase and oxyhaemoglobin, and an absolute tissue saturation, the tissue oxygenation index or TOI. There was a lack of previous literature on the relation between oxygen saturation and TOI, as validation work had been performed in neurosurgical theatres where SaO_2 was kept constant under anaesthetic. In this setting it was possible to define a TOI change and then group subjects as to whether TOI changed or not, basically an all or none phenomenon. This technique could not be applied in OSA where arterial saturation changes defined the condition. Another problem was comparison of values between subjects, where baseline values were known to vary quite significantly between subjects. The sheer volume of data produced posed other problems, as unlike in other clinical monitoring systems (eg polysomnography, ECG monitoring etc) automated processing to identify noise, artifact and periods of interest have not yet been developed, and it was basically down to us to try and identify what the periods of interest were. Our medical physics and physiology collaborators were accustomed to an experimental set up where a stimulus is applied and responses in other parameters are recorded, and then replicate stimuli are performed and responses averaged to give results to an experimental question. The study of sleep apnoea in adults is essentially observational, in that the subject initiates the stimulus (upper airway obstruction) and then this initiates changes in various physiological parameters which can be recorded. We are lucky in that multiple episodes naturally occur, and that these are similar in a subject, however the repetitive episodes are not identical and vary in duration and severity. Hence it is not particularly useful to model the "wiggly lines" as though they were a regular waveform with superimposed noise.

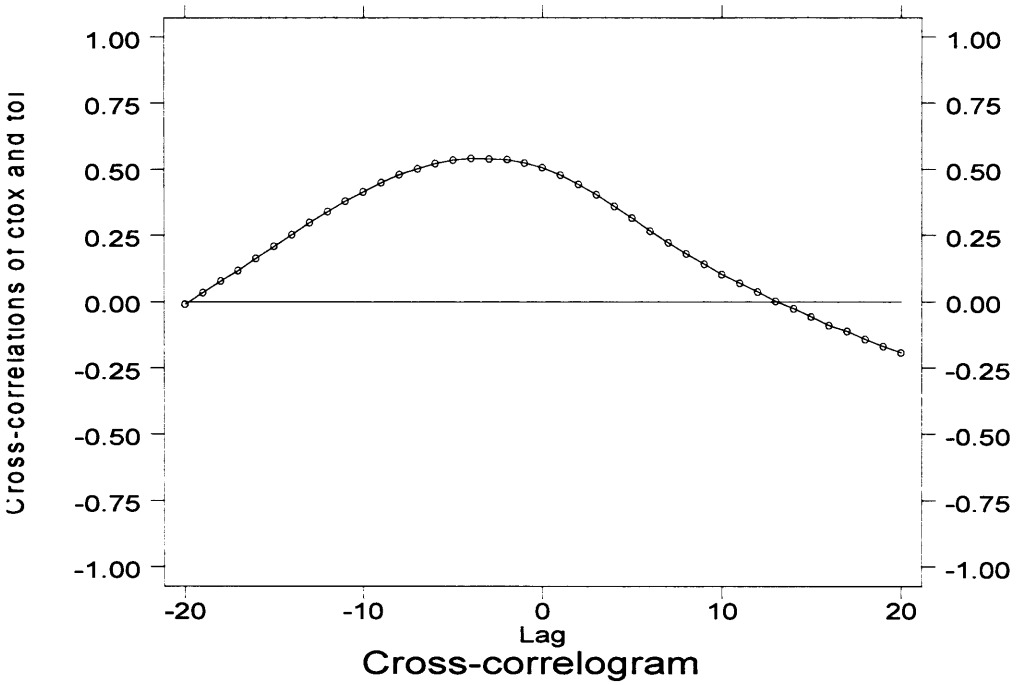
My main aim in the validation study was to quantify changes in the various parameters and to see whether they were related to changes in other parameters which occurred

during apnoea (as if they were it implied that the changes we were measuring were real, rather than just being noise). At best I could define an association between the parameters. I might suggest causation as an explanation of these associations because of biological plausibility (eg association of cerebral blood flow and cerebral oxygenation) however our experimental setup did not allow us to prove causation because it was observational and I was not able to manipulate variables.
Possible ways of comparing the traces included direct comparison of the digital wave forms using techniques of time series analysis and lagged correlation, two point comparisons and cumulative averaging of changes during apnoea.

5.1 COMPARISON OF WAVE FORMS

Some attempts were made to compare the traces using lagged correlation. However because of the intermittent nature of the apnoeas, their non-identical nature, and our lack of the necessary mathematical knowledge, this did not seem to be a useful way of comparing subjects, or reaching conclusions on the combined data. We were able to obtain the lag of maximum correlation and the maximum correlation coefficient between two parameters for short periods of repetitive apnoeas. It was unclear how to select the data to use for this analysis or how to use the results. This analysis technique was therefore not used further. The following figure (Figure 16) illustrates correlations at different time lags between TOI and cytox for raw data illustrated in Table 3, showing maximum correlation of approximately 0.5 at a cytox lag of 4s behind TOI.

Figure 16. Lagged correlations between cytox and TOI for subject 1 during consecutive apnoeas
This shows correlations of the ctox and TOI traces for lags between -20 and +20s, for a 200s period during a run of apnoeas. Ctox = cytochrome oxidase; TOI = tissue oxygenation index.



5.2 TWO POINT CORRELATIONS

This technique involves defining an episode of interest (apnoea) and then recording the maximum and minimum values of defined parameters associated with the apnoea. The change in each parameter for that apnoea is then calculated. These changes can be compared between different parameters for individual apnoeas, and also averaged for each subject. The polysomnography software uses an algorithm to define the oxygen saturation dip associated with an apnoea. We used this value in analysis, and also manually calculated dips (or rises) in most of the recorded parameters in the different validation studies. We were able to do this on the polysomnography TOI trace by visually identifying the pre-apnoea maximum and post-apnoea minimum on the TOI trace. Clicking on the trace with the computer cursor at these points enabled us to read off the TOI values which were recorded in a table. By the time we came to do the prospective study using full night polysomnography, we were able to use the SaO_2

analysis algorithm to calculate TOI dips for us. For the other traces not on the polysomnography system (cytox, total haemoglobin, and CBFV, ABP) we illustrated the data series graphically in Excel® (Microsoft Office 95, Microsoft Corporation, USA) defined apnoea, and again read off consecutive maxima and minima by clicking on the visually identified points which resulted in the value appearing in a text box. The data was illustrated sequentially in sections of 200-300 observations for each subject. The maxima and minima read off were than tabulated in a further excel® file and then combined in a stata dataset for manipulation.

The following table (Table 3) illustrates the data as obtained from the NIRO300.

Table 3. Data obtained each second during apnoeas from one subject

(elpsec = elapsed seconds, O2Hb = oxyhaemoglobin, HHb = deoxyhaemoglobin, Ctox = cytochrome oxidase, ctox10 = multiplied by 10, TOI = tissue oxygenation index. THb = O2Hb + HHb = total haemoglobin. Units for the chromophores O2Hb, HHb, Ctox and THb are μM from an arbitrary baseline, and for TOI are % saturation)

elpsec	O2Hb	HHb	Ctox	TOI	THb	Ctox10
4401	1.97	10.87	1.38	67	12.84	13.8
4402	4.99	10.35	1.64	66	15.34	16.4
4403	6.14	13.52	0.6	66	19.66	6
4404	5.83	13.64	0.87	66	19.47	8.7
4405	2.96	14.17	0.28	65	17.13	2.8
4406	-3.34	13.43	0.98	65	10.09	9.8
4407	-3.85	13.41	1.32	64	9.56	13.2
4408	-2.39	16.63	0.79	64	14.24	7.9
4409	-0.18	18.38	0.77	63	18.2	7.7
4410	0.14	19.89	0.51	64	20.03	5.1
4411	-0.73	21.96	1.17	63	21.23	11.7
4412	-3.38	21.18	1.82	63	17.8	18.2
4413	-7	22.38	0.87	62	15.38	8.7
4414	-5.31	23.09	0.88	63	17.78	8.8
4415	-2.61	25.47	0.05	62	22.86	0.5
4416	-2.15	26.78	1.12	63	24.63	11.2
4417	-0.57	28.64	0.33	62	28.07	3.3
4418	-3.55	27.51	1.39	61	23.96	13.9
4419	-3.57	26.49	0.54	62	22.92	5.4

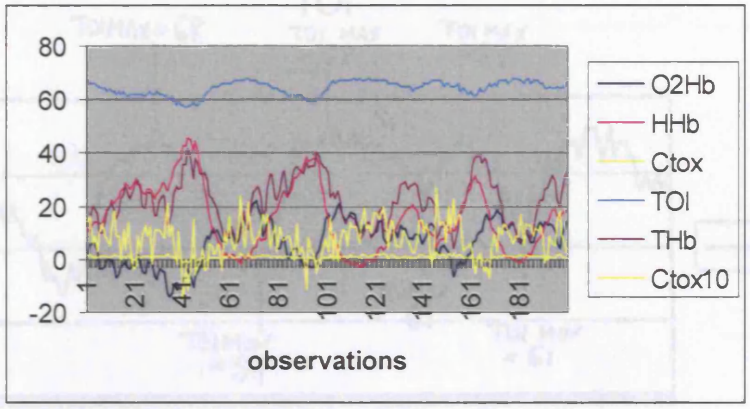
4420	-2.25	27.84	-0.34	62	25.59	-3.4
4421	-1.12	30.28	-0.23	62	29.16	-2.3
4422	1.49	28.05	0.84	62	29.54	8.4
4423	-1.65	27.7	0.26	62	26.05	2.6
4424	-4.81	24.78	0.93	62	19.97	9.3
4425	-5.31	24.7	1.3	61	19.39	13
4426	-1.33	26.14	0.87	62	24.81	8.7
4427	-1.04	25.99	1.21	63	24.95	12.1
4428	-1.77	25.67	-0.18	62	23.9	-1.8
4429	-6.39	22.57	1.08	62	16.18	10.8
4430	-7.79	24.26	1.1	63	16.47	11
4431	-3.91	25.8	1.08	62	21.89	10.8
4432	-4.79	28.42	0.88	62	23.63	8.8
4433	-4.51	28.6	0.81	61	24.09	8.1
4434	-12.87	25.9	2.09	61	13.03	20.9
4435	-14.35	27.57	0.87	60	13.22	8.7
4436	-12.77	31.05	1.28	61	18.28	12.8
4437	-9.25	33.53	0.52	60	24.28	5.2
4438	-9.11	36.22	-0.18	58	27.11	-1.8
4439	-10.56	36.86	1.05	59	26.3	10.5

This data was illustrated in Excel® in order to read off maxima and minima from each trace.

Figure 17 shows the data from table 3 shown as traces on an Excel® graph. It should be noted that it was necessary to multiply the cytox trace by a factor of 10.

Figure 17. Data from table 3 graphically illustrated in format used to read off maxima and minima

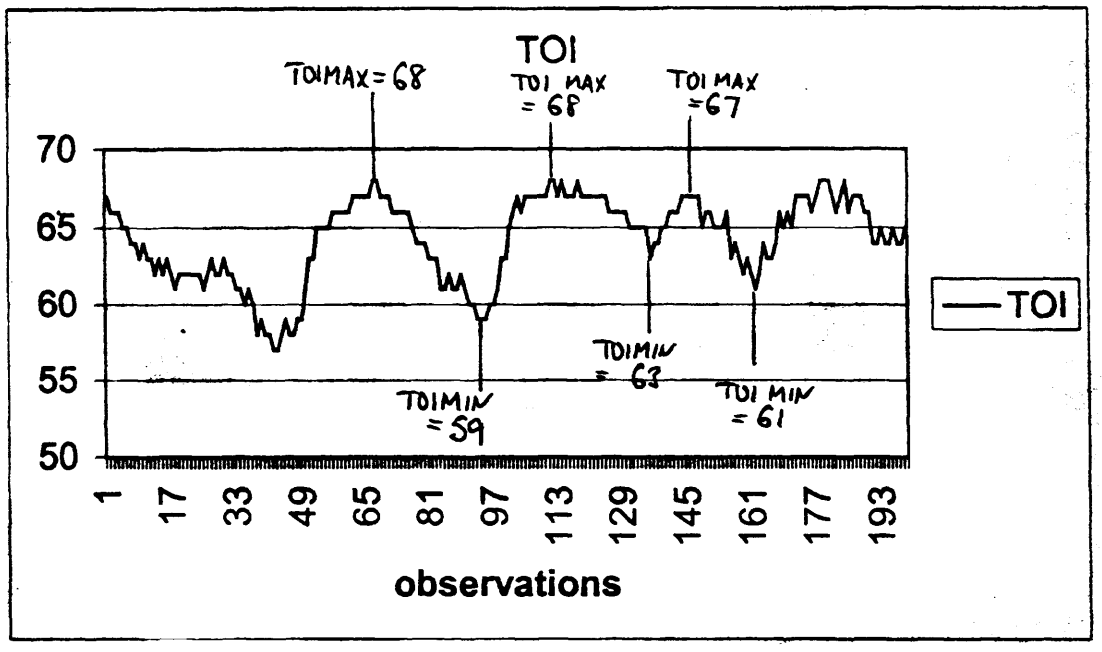
The data is consecutive observations obtained each second from one subject during apnoeas. O2Hb = oxyhaemoglobin, HHb = deoxyhaemoglobin, Ctox = cytochrome oxidase, ctox10 = multiplied by 10, TOI = tissue oxygenation index. THb = O2Hb + HHb = total haemoglobin. Units for the chromophores O2Hb, HHb, Ctox and THb are μM from an arbitrary baseline, and for TOI are % saturation)



When the cursor is placed over a trace in Excel® a box appears with the value of the points making up the trace. Minima and maxima may be identified by looking at the trace and the values confirmed using the cursor in this way. Values for TOI were identified first as shown in the figure (Figure 18). A maximum and consecutive minimum defined an apnoea.

Figure 18. TOI trace with consecutive maxima and minima marked

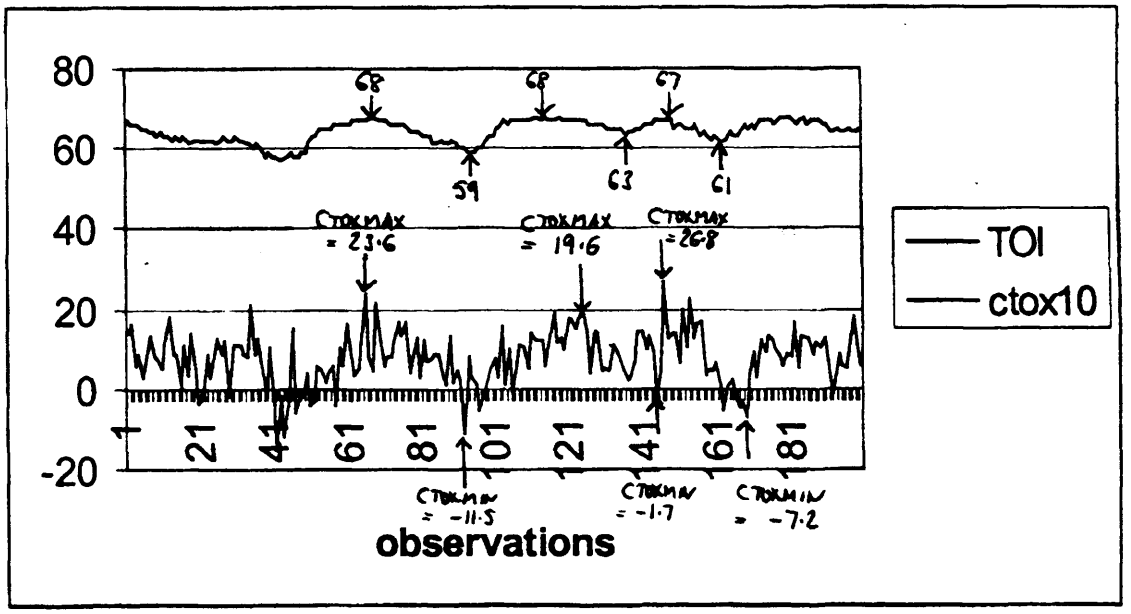
(Units for TOI on the y axis are % saturation and for observations on the x axis are seconds. TOI = tissue oxygenation index, toimax = maximum TOI for that apnoea, toimin = minimum TOI for that apnoea).



The corresponding cytochrome oxidase maxima and minima were similarly read from the Excel® trace (See Figure 19). In order to visualise the correct values it was necessary to illustrate the trace multiplied by a factor of 10.

Figure 19. TOI and cytochrome oxidase traces with cytochrome oxidase maxima and minima corresponding to TOI maxima and minima marked.

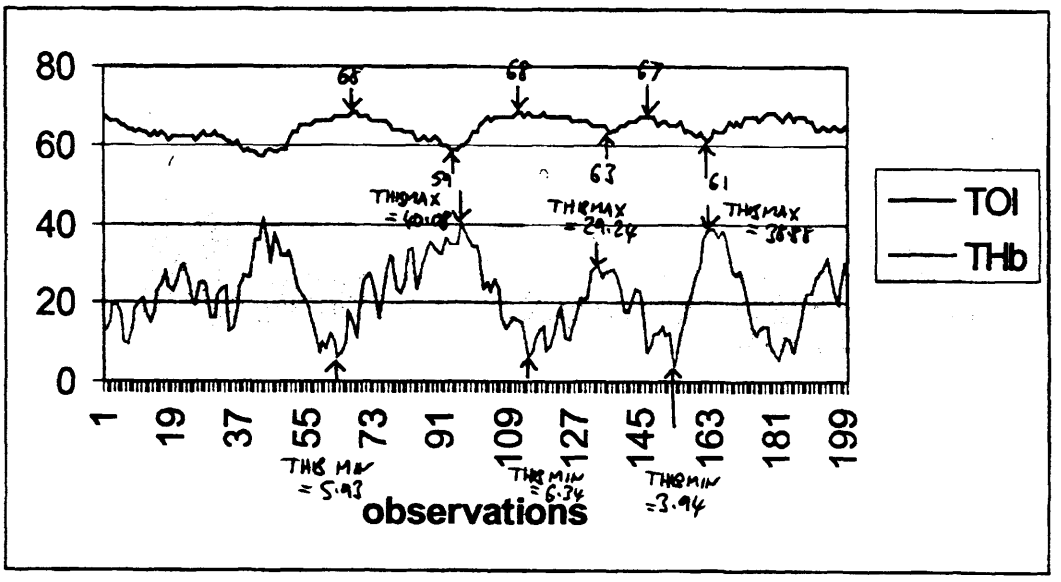
(TOI = tissue oxygenation index, ctox10 = cytochrome oxidase multiplied by 10, ctoxmax is maximum ctox10 for that apnoea, and ctoxmin = minimum ctox10 for that apnoea. Corresponding maxima and minima for TOI are also marked. Units on the y axis are %saturation for TOI and μM from an arbitrary baseline for ctox10, and units on the x axis are seconds.)



A similar technique was used to read off THb maxima and minima (Figure 20). As studies of cerebral haemodynamics in OSA show that there is an initial fall in cerebral blood flow followed by a surge at the end of apnoea, it was assumed that the THb minimum preceded the maximum for each apnoea.

Figure 20. THb mimima and maxima corresponding to TOI maxima and minima

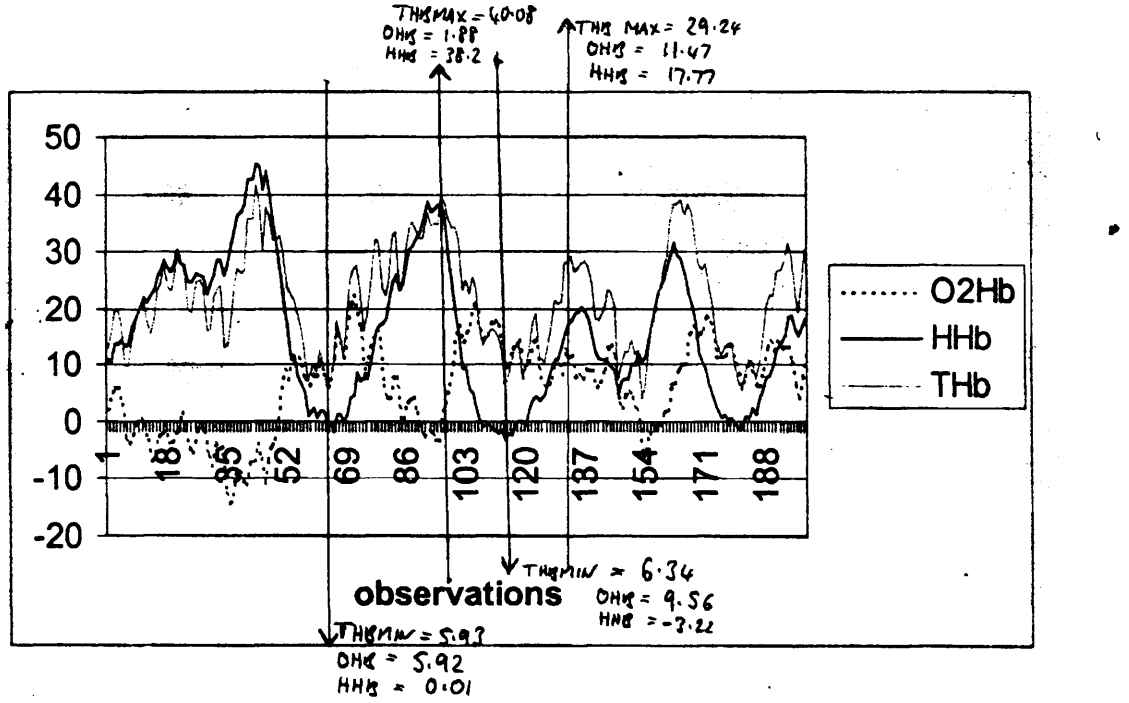
(TOI = tissue oxygenation index,THb = sum of oxygenated and deoxygenated haemoglobin, THbmax is maximum THb for that apnoea, and THbmin = minimum THb for that apnoea. Corresponding maxima and minima for TOI are also marked. Units on the y axis are %saturation for TOI and μM from an arbitrary baseline for THb, and units on the x axis are seconds.)



Ohbratio was calculated as the change in Ohb which occurred during the THb surge, expressed as a fraction of the THb change. In order to calculate it it was necessary to subtract the Ohb value when THb was minimum from the Ohb value when THb was maximum. These values were actually obtained from lists of the raw data once the values and timepoints for THb max and THb min had been read off as shown in the preceding figure (Figure 20). The next figure (Figure 21) shows how the THb values are obtained from the sum of the Ohb and HHb values at that time point so that Thbmax = ohbthbmax + hhbthbmax.

Figure 21. Example of values of Ohb and HHb at the timepoints of maximum and minimum THb

(OHb = oxygenated haemoglobin, HHb = deoxygenated haemoglobin, THb = sum of OHb and HHb, THbmax = maximum THb for that apnoea, and THbmin = minimum THb for that apnoea. Units on the y axis are μM from an arbitrary baseline for OHb, HHb and THb, and units on the x axis are seconds.)



Maxima and minima read off from the traces as illustrated in the figures (Figures 18 – 21) were tabulated as shown in table 4.

Table 4. Minima and maxima data obtained from eg figure 17.

(TOI = tissue oxygenation index, ctox = cytochrome oxidase, toimax and toimin = maximum and minimum TOI for that apnoea, ctox max and ctox min = maximum and minimum ctox for that apnoea, THb = total haemoglobin, THbmax and THb min are maximum and minimum THb for that apnoea. Ctox is multiplied by 10. OHbTHbmax etc is the absolute value of OHb when THb is maximum and is used in the calculation of Ohbratio. Units fro chromophores are μM from an arbitrary baseline.)

Toimax %	Toi min/%	Ctox max/μM	Ctox min/μM	THb max /μM	THb min /μM	OHbTHb max/μM	HHbTHb max/μM	OHbTHb min/μM	HHbTHb min/μM
68	59	23.6	-11.5	40.08	5.93	1.88	38.2	5.92	0.01
68	63	19.6	-1.7	29.24	6.34	11.47	17.77	9.56	-3.22
67	61	26.8	-7.2	38.88	3.94	10.43	28.45	-6.35	10.29
68	64	16.6	-1	31.46	5.44	13	18.46	6.82	-1.38
67	58	18.6	-11.2	35.75	9.66	17.17	18.58	-1.04	10.7
71	63	23.4	-4.8	43.35	15.78	16.18	27.17	-9.26	1.91
70	59	20.8	-8.4	43.94	11.22	0.29	43.65	16.22	-5
69	59	22	-14.9	41.96	9.65	11.34	30.62	12.03	-2.38
69	65	23.6	-5.5	32.14	12.32	24.58	7.56	15.2	-2.88
70	55	23.7	-11.7	43.48	3.81	-1.41	44.89	14.11	-8.21
71	56	18.3	-6.6	60.3	18.06	3.33	56.97	24.17	-6.11
71	56	26.6	-2.1	51.62	12.18	-1.55	53.17	18.1	-5.92
70	56	25.5	1.1	53.24	11.8	1.49	51.75	19.21	-7.41
70	61	24.2	-1.4	30.85	13.5	4.68	26.17	18.22	-4.72
70	53	25.8	-4.2	45.25	1.42	8.96	36.29	-3.41	4.83
70	56	26.9	-1.9	40.32	8.88	6.55	33.77	16.46	-7.58
69	56	29.2	-1.3	50.5	7.02	11.5	39	10.74	-3.72
71	60	35.6	6	41.62	9.45	11.58	30.04	21.53	-12.08
71	56	29.1	5.8	54.63	6.66	10.65	43.98	19.36	-12.7

These tables were entered into a database. Changes in the parameters during each apnoea (eg TOImax – TOImin) were calculated within the database and used in analysis. The choice of statistical analysis used is discussed in section 5.5.

5.3 CUMULATIVE AVERAGING

Cumulative averaging is an analysis technique derived from the idea that sequential apnoeas may be viewed as a repeated "experiment" in which replications are averaged to give the usual response. It differs from 2 point analysis in that sequences of raw data are used, but because those sequences are selected as runs of similar consecutive apnoeas less information is lost in averaging than in, for example, lagged correlations. The technique involves identifying for a subject a run of consecutive apnoeas of similar length, usually between 8 and 15. Taking TOI or if available SaO_2 as the defining variable, individual apnoeas between consecutive TOI minima are separated and "lined up" together on an Excel® spread sheet. Because of the saw tooth shape of the saturation traces it is much easier to define the precise minimum as an end point than the maximum – however this does lead to an unconventional representation of an apnoea.

For example a TOI trace illustrated in Fig 22 may be "lined up" as consecutive apnoeas as shown in Table 5, and graphically in Figure 23.

Figure 22. TOI trace during consecutive apnoeas in one subject

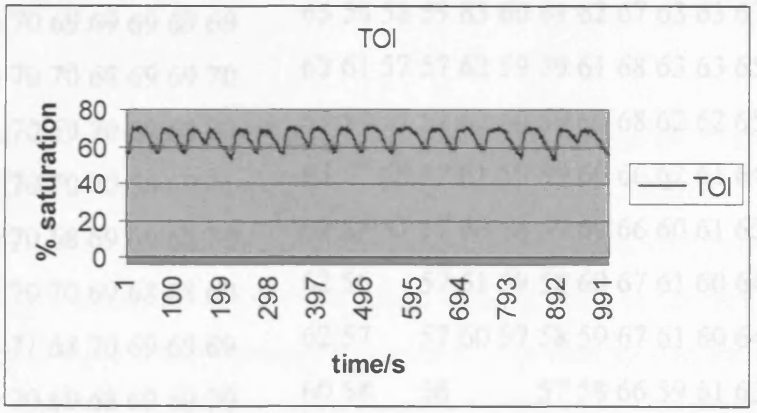
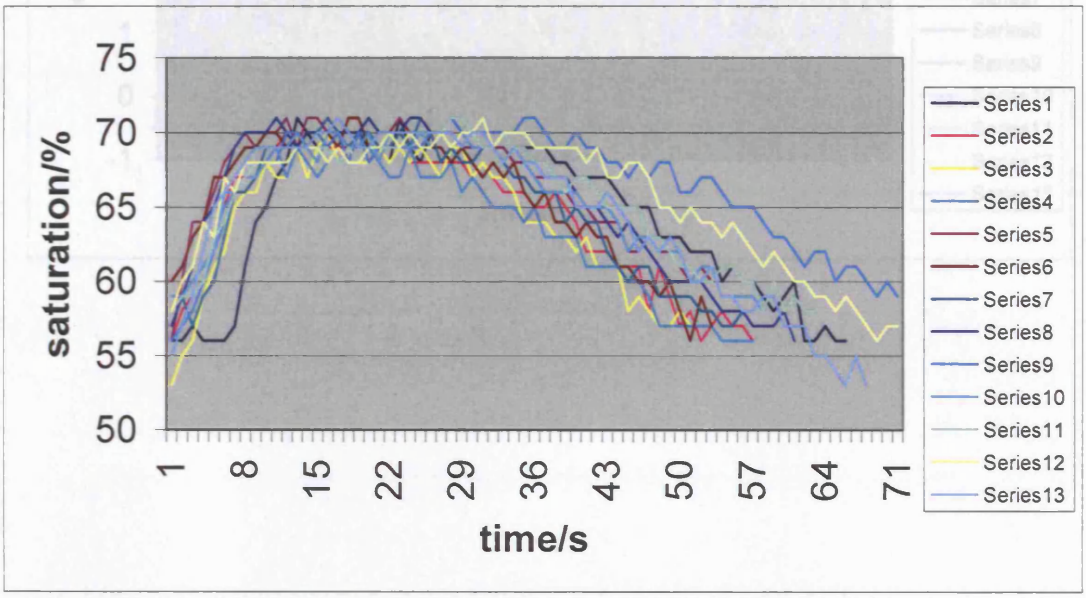


Table 5. 13 consecutive apnoeas "lined up" together, each vertical column represents consecutive (every s) TOI readings (in % saturation) for a single apnoea as shown in figure 22

1	2	3	4	5	6	7	8	9	10	11	12	13
56	56	53	56	56	60	57	57	56	59	58	58	55
56	58	55	57	60	61	59	59	57	59	59	60	57
57	59	56	59	64	63	57	61	58	60	59	61	59
56	60	59	60	64	64	59	64	60	61	60	64	62
56	63	61	63	66	67	60	65	62	62	63	63	65
56	65	62	65	68	67	63	67	64	66	64	67	66
57	67	65	66	69	68	66	69	66	66	66	66	67
61	67	66	67	70	69	66	70	67	67	67	68	68
64	67	66	67	69	69	67	70	68	67	68	68	69
65	69	68	69	70	70	69	70	68	68	68	68	69
67	69	67	69	70	70	69	71	68	69	68	68	69
68	70	67	67	71	69	69	70	70	69	68	68	69
71	69	69	69	69	70	69	69	70	70	69	69	69
70	69	67	68	71	69	70	70	69	69	69	69	69
69	70	69	67	71	70	70	70	70	68	69	69	70
69	69	70	68	70	70	71	70	69	70	69	68	70
69	69	68	69	70	69	70	70	70	70	68	69	71
69	69	69	68	70	71	69	70	68	69	69	68	70
70	68	68	68	70	71	70	70	70	69	68	68	69
69	69	68	69	71	69	70	71	68	70	69	69	69
69	69	69	68	70	70	69	70	69	68	69	69	70
68	69	68	67	70	70	69	70	69	70	69	70	70
71	69	69	67	71	69	70	70	69	69	69	69	70
69	68	68	69	70	69	69	71	69	69	70	70	70
68	68	69	67	69	70	71	71	69	70	70	69	70
70	68	68	67	70	69	70	70	70	69	70	69	70
70	68	67	67	70	69	68	70	70	70	70	70	70
71	68	69	68	70	68	69	70	71	69	71	69	70
70	68	69	66	69	69	68	69	70	70	71	70	69
70	67	67	67	69	68	68	70	70	69	70	70	70
71	68	68	66	69	67	69	70	70	69	69	71	70
69	67	67	65	69	68	69	69	70	69	69	69	69
70	66	67	65	69	67	68	68	70	68	70	70	68
69	66	66	65	68	68	67	69	70	69	69	70	69
69	66	64	64	68	66	67	68	71	68	69	70	68
69	65	64	65	67	65	66	68	71	67	68	69	68
69	65	64	63	67	66	66	68	70	66	68	69	67
68	66	63	63	67	64	66	67	69	66	67	69	67
68	65	63	63	66	64	64	67	69	66	66	69	67
67	64	62	63	65	63	65	66	70	66	67	69	65
67	62	63	61	65	64	64	65	69	65	67	68	65
67	62	61	61	64	63	64	65	69	65	66	69	65
67	62	61	61	64	63	62	64	68	65	65	67	66
66	61	61	61	64	61	61	63	68	64	65	67	65
65	61	58	60	62	61	60	64	67	62	65	68	64
65	61	59	60	62	60	61	63	68	63	65	68	62
65	58	58	59	63	60	61	62	67	63	63	67	63
63	61	57	57	62	59	59	61	68	63	63	65	62
63	59	57	57	62	60	59	60	68	62	62	65	63
63	57	58	57	61	58	59	60	66	62	61	64	62
62	58	57	57	60	56	59	60	66	60	61	65	60
62	56		57	61	59	58	60	67	61	60	64	60
62	57		57	60	57	58	59	67	61	60	64	61
60	58		56		57	58	66	59	61	63	59	
61	57		56		57	58	65	59	61	64	59	
60	57		56		58	58	65	59	60	63	58	
60	56		56		57	57	65	59	60	62	58	
59						57	64	58	58	61	59	
58						57	63		60	62	59	

59	58 63	58 61 57	56	60	58 54
60	56 62	59 60 57	56	61	59 53
56	61	58 60 57		61	58 55
56	62	58 59 55		60	57 53
57	62	59 55			

Figure 23. Table 5 illustrated graphically, showing TOI readings for 13 apnoeas on a single graph, each data series represents an apnoea.



The 13 values are then averaged at each time point to give the TOI trace for an average apnoea. This is repeated for the other parameters. In order to get the changes synchronized, the observation number at the beginning and end of each section of the TOI data as shown in table 5 is recorded, and the sections of data for other parameters are defined by these times irrespective of the trace appearance. For example the following graph (Figure 24) illustrates cytochrome oxidase changes for the same data stretch. Once all the sections of data have been averaged they can then be combined on a graph to show average changes in these parameters in a particular subject (Figure 25). Clearly not all subjects have a series of consecutive apnoeas appropriate for this analysis, as it cannot be used for isolated apnoeas because changes in the parameters other than the defining one (TOI or SaO_2) would be difficult to interpret.

Figure 24. Cytochrome oxidase changes during consecutive apnoeas, defined by TOI dip.

Each data series is taken from a different apnoea, using the TOI minimum timepoint as the initial timepoint. TOI = tissue oxygenation index, Ctox = cytochrome oxidase, units for ctox are µM from an arbitrary baseline.

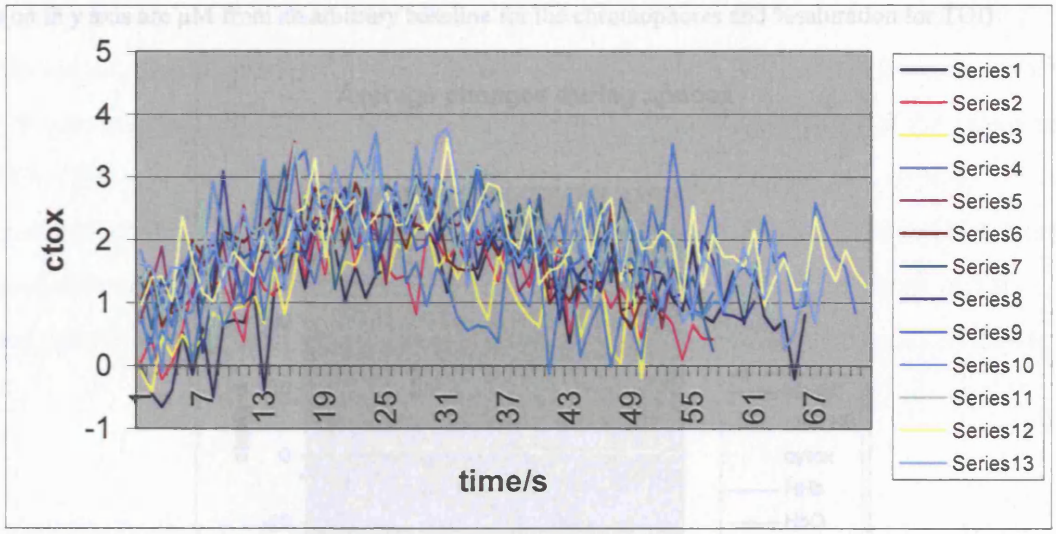
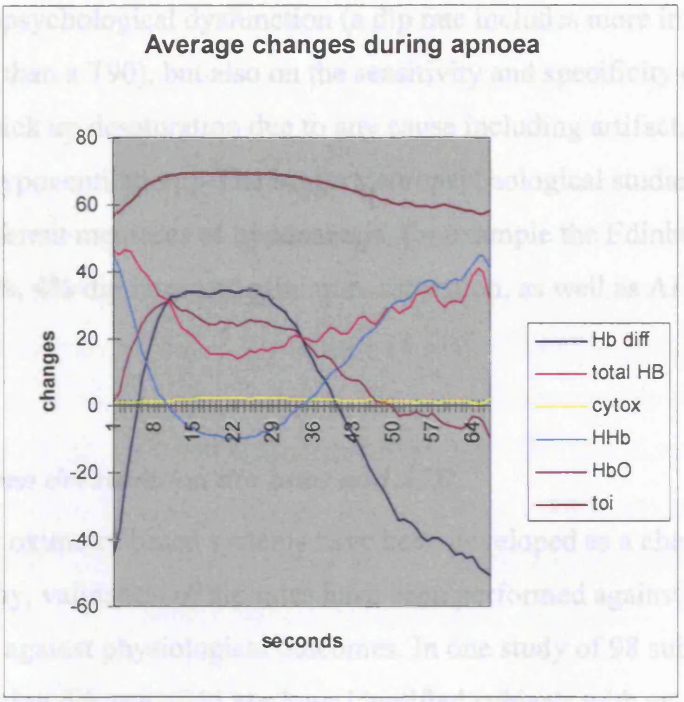


Figure 25. Cumulative average of changes during 13 apnoeas in one subject

(Initial timepoint is defined by TOI minimum, Hbdiff = OHb-HHb, Total HB = OHb + HHb, cytox = cytochrome oxidase, HHb = deoxyhaemoglobin, HbO = oxyhaemoglobin, TOI = tissue oxygenation index, units on th y axis are μM from an arbitrary baseline for the chromophores and %saturation for TOI)



5.4 OVERNIGHT SUMMARY MEASURES FOR TOI

The previous data analysis was based on analysis at the level of individual apnoeas in order to fully characterize the information available from the NIRO300. The aim of this pilot work was to validate the use of the NIRO300 as a measure of cerebral oxygenation in OSA so that it could be used in a prospective study looking at the relationship between neuropsychological function and cerebral oxygenation in subjects with OSA before and after treatment.

5.4.1 Summary measures from pulse oximetry

In order for the NIRO300 to be used in this study summary measures needed to be developed from overnight recordings that could be compared between subjects. This is a similar problem to the analysis of overnight pulse oximetry readouts for sleep studies, and

summary measures are computed by sleep study systems to allow meaningful comparison. For example the visilab system computes diprates, time spent below a specified saturation, mean saturation, absolute minimum saturation, and mean minimum saturation, all from a record of serial oxygen saturation against time. It is not clear which of these values is most useful in studies of neuropsychological function in OSA as it will depend not only on the mechanism of neuropsychological dysfunction (a dip rate includes more information about sleep fragmentation than a T90), but also on the sensitivity and specificity of the measures for OSA (T90 will pick up desaturation due to any cause including artifact, overlap syndrome, obesity hypoventilation.) The bigger neuropsychological studies in OSA have included several different measures of hypoxaemia, for example the Edinburgh group routinely use 2%, 3%, 4% dip rates and minimum saturation, as well as AI and AHI (64, 68).

Relationship between desaturation dip rates and AHI

Because historically oximetry based systems have been developed as a cheap alternative to full polysomnography, validation of dip rates have been performed against AHI as a gold standard rather than against physiological outcomes. In one study of 98 subjects (133) a 2% oxygen desaturation dip rate of 15 per hour identified subjects with an AHI of 15 per hour with sensitivity 65% and specificity 74%, a 3% dip rate of 15 had sensitivity 51% and specificity 90%, and a 4% dip rate had sensitivity 40% and specificity 98%. The British Thoracic Society therefore chose to specify a 4% dip rate of 15 dips per hour with baseline SaO_2 >90 as diagnostic of OSA requiring treatment and this has been validated in 69 subjects against polysomnography with a sensitivity of 31% and specificity 100% (134). I quote these papers just to emphasize that the selection of clinically useful dip rates for SaO_2 is based only on comparison with a different sleep study measure (AHI) which is currently used to define OSA, and so it is difficult to derive from this what dip rates to use for TOI.

Other measures of desaturation

The degree of desaturation associated with an apnea or hypopnea is highly variable and depends on lung volume, obesity, age, associated lung disease, chemoreceptor sensitivity, sleepstage etc. Apnoea at low lung volumes is associated with severe SaO_2 desaturation in normal awake subjects (135). The rate of oxyhaemoglobin desaturation is greater in

obstructive than non-obstructive apnoeas in animals and this may be due to increased tissue oxygen consumption (136). Apnoea duration can be lengthened by administration of oxygen or shortened by administration of carbon dioxide suggesting a role for chemoreceptors in apnoea termination (137). Because of these variations in oxygen desaturation during an apnoea, measures of OSA severity based on oxygen saturation do not necessarily correlate with AHI. If arousals are the main determinant of altered daytime functioning in OSA, then basing severity on AHI alone is appropriate, however many studies of neuropsychological dysfunction show an independent effect of hypoxaemia. The most sensitive measure of oxygen desaturation would be an "area under the curve" integration of the oximetry trace from a baseline. Chesson et al (138) developed a saturation impairment time (SIT) on the principle of integrating duration and severity below varying threshold saturations. They compared SIT indices in a group of subjects with OSA and a group of normals and found a significant difference. However they found considerable variation in SIT index in subjects with similar RDIs and vice versa. They did not proceed to look at the relationship between this new measure and any outcome measure like neuropsychological function to reinforce their conclusion that this new measure may provide complementary information in assessing the severity of OSA.

5.4.2 Possible TOI derivatives to be used in study analysis

Three main methods are used to measure oxygen desaturation in sleep studies, and potentially can be adapted for use with TOI tissue saturation:

Absolute values These include absolute minimum saturation and average saturation. Because of the variation between subjects in baseline TOI, these are less useful in TOI measurements than saturation. Also the absolute minimum is susceptible to artifactual errors due to transient loss of contact.

Dip rates These record the rate at which a specified desaturation occurs (usually calculated by algorithm acting on serial saturation data assuming this desaturation due to apnoea/hypopnoea).

Measures of desaturation severity These include T90 (time spent below a specified saturation) or AUC measures (time multiplied by extent of desaturation).

5.4.3 TOI Dip rate calculation

Theoretical considerations

One example of an algorithm to calculate a dip rate is quoted below – "The algorithm sequentially scanned each recorded oxygen saturation value (1Hz). Whenever a drop in a sampled oxygen saturation value was detected the programme assigned an event marker to that reading. When an increase in oxygen saturation was detected, the programme determined if at least 3 consecutive event markers – that is, three consecutive falls in oxygen saturation – were present prior to this rise. If this criterion was met and one of the event markers was associated with an oxygen saturation value > or = 4% lower than the baseline oxygen saturation, then a (dip) was designated. Baseline oxygen saturation was calculated as a moving time average (the mean of the top fifth percentile of oxygen saturation values over the five minutes preceding the event)" (139).

We initially planned to use a similar algorithm to carry out TOI dip rate analysis. Because of the amount of noise inherent in the TOI trace, (and the lack of previous experience of use of the NIRO for this purpose along with minimal computer programming experience in the main investigators) it was not easy to develop a simple computer programme to provide a useful dip rate from the digital output, despite attempts by two people with programming experience. Hence the decision was made to use the pre-existing polysomnography analysis software which enables calculation of an apnoea-associated dip rate of a percentage which is specified by the operator. Although the dip-rates produced by sleep study oximetry systems like the visilab are not apnoea-associated but are calculated using an algorithm that will pick up any fall in saturation of the specified amount whether or not it is associated with an apnoea/hypopnoea, an apnoea/hypopnoea associated dip rate is a purer physiological concept for comparison.

Conventionally when respiratory analysis is carried out on the Compumedics® system the user specifies a time lag for the SaO_2 trace (30s by default), and the program scans from the (end of the apnoea + lag) back to the (beginning of apnoea + lag) to look for the minimum saturation for that apnea (ie the computer programme adds 30s to the timepoint at the end of the apnea and then scans back from this timepoint to find the minimum saturation, stopping scanning at the timepoint 30s after the beginning of the apnea, so that the time scanned is the same as the apnea duration at a time lag of 30s). The user also inputs the SaO_2 percentage drops to be used for definitions of apnoea and hypopnoea

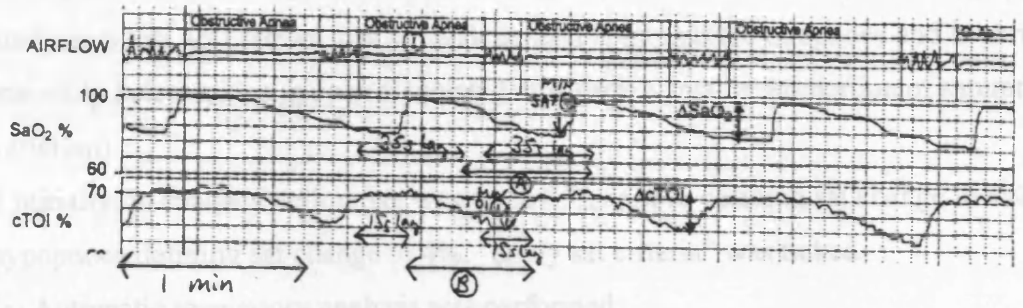
respectively, currently set at 1% and 4%. Also of relevance is the minimum duration of an event which is internationally accepted as 10s (invariable within the program). If the names of the SaO_2 and TOI channels are transposed and respiratory analysis is repeated the program will calculate minimum TOI and TOI dip for each events, but will not produce a report from the altered data. A dip rate can be produced by manually scanning through the study and recording the dips for computer scored apnoeas. To provide a comparable result for the SaO_2 trace the same technique was used for that as well, ie without later manual scoring, and ignoring "unsure" events.

Choice of lag for SaO_2 and TOI

Lags from our validation study are published as follows: "The cTOI and SaO_2 nadir occurred at 9.5 (± 2.8) sec and 28.7 (± 5.0) sec (range 6.9 - 15.9 vs. 24.7 - 38.7 sec; $p < 0.001$) after the end of an apnoea/hypopnoea." (1). For this paper nadirs were measured manually by visual inspection. As expected the difference between TOI and SaO_2 is about 20s, the circulation time. Bearing in mind that the program scans back from the (end of apnoea + lag) to the (beginning of apnoea + lag) to reach the minimum and that the minimum apnoea duration is 10s, the use of lags of 35s for SaO_2 and 15s for TOI will obtain the maximum correct nadirs without resorting to varying the lags for each subject (because the computer will scan back from 35 s after the apnoea to at least 25s after the apnoea for SaO_2, and from 15s to 5s for TOI, thus encompassing most of the range). Figure 26 illustrates the way the lags are used on the polysomnography trace to obtain minimumum values for TOI and SaO_2.

Figure 26. Figure showing lags used to calculate minimum TOI and SaO_2 for dip rates

This is part of an annotated polysomnography trace with SaO_2 = oxygen saturation by pulse oximetry and cTOI = tissue oxygenation index. Minsat = minimum SaO_2 for that apnoea and minTOI = minimum TOI for that apnoea. The annotation shows that for apnoea 1 the computer scans from the end of the apnoea plus 35s back to the beginning of the apnoea plus 35s (time period A in the diagram) on the SaO_2 trace to find minimum saturation 1, and from the end of the apnoea plus 15s back to the beginning of the apnoea plus 15s (time period B in the diagram) on the TOI trace to find minimum TOI 1.



Choice of percentage saturation drops for dip rates

For SaO_2 the 4% dip rate is supported by the literature as correlating best with AHI (133), and is also conventionally accepted.

For TOI there is no precedent. Again from our previous paper "Mean event related dips in TOI ranged from 1.4 to 6.85%, where mean oxygen desaturation dips ranged from 3.8 to 22.3% in the 13 subjects", ie TOI dips were less than SaO_2 dips (1)(109). We calculated event related 2% and 4% dip rates for this data (1036 apnoeas), published only in abstract form (140), omitted from the published paper because of reviewers' objection to the arbitrary selection of 2% and 4%. To quote from an early draft "2% cTOI dip rates ranged from 3.5 to 94, and 4% from 0 to 77, where corresponding AHI ranged from 14.6 to 97.6. A significant relationship was observed between the number of apnoea- associated 2% TOI dips per hour and the AHI ($c = 0.95$, $p < 0.01$). The 4% TOI diprate/hr also correlated with the AHI ($c = 0.84$, $p < 0.01$), and correlated better than AHI with the mean min. SaO_2 ($c = 0.71$, $p < 0.01$) and the % sleep time spent below 91% SaO_2 ($c = 0.775$, $p < 0.01$), and below 86% SaO_2 ($c=0.61$, $p<0.05$)." Correlations with AHI (apnoea hypopnoea index) are

to be expected because these dip rates are apnoea associated by definition. We calculated both 2% and 4% apnoea associated TOI dips for the prospective study as we had no evidence that one was any more relevant than the other.

Practical protocol

This protocol explains exactly the commands used in the compumedics® software to calculate TOI and SaO_2 dip rates in an equivalent and reproducible manner. It should be read in conjunction with the Compumedics® analysis manual(see appendix).

1.Files were restored to hard disc.

2.Only baseline studies prior to CPAP treatment(n=58) were used (as on CPAP, automated analysis is less accurate as loss of mask contact is interpreted as apnoea and is normally manually deleted; also apnoea associated dips form a smaller proportion of saturation variation).

3.Initially, in analysis option, lag was set to 35s, apnoea defining sat change to 4%, hypopnoea defining sat change to 4%, "apply sat criteria" was ticked.

(a) Automatic respiratory analysis was performed

(b) 5min screens were scanned through starting at epoch 1

(c) A 5min screen was omitted if loss of contact of either SaO_2 probe or TOI probe for >10s

(d) Sleep stage at start of screen was recorded

(e) Each apnoea/hypopnoea was "clicked on" and sleep stage, minimum saturation and saturation dip were recorded. Unsures were ignored.

(f) Dip rate was obtained by dividing total number of events by time asleep. Mean minimum sat and mean dip were calculated.

5."Config poly" option was entered and SaO_2 channel was renamed TOI and vice versa. In analysis option lag was set to15s, apnoea defining sat change to 2%, hypopnoea defining sat change to 2%, "apply sat criteria" was ticked.

Steps (a) to (f) were repeated.

5. 4% dip rates were obtained from 2% dip rate data.

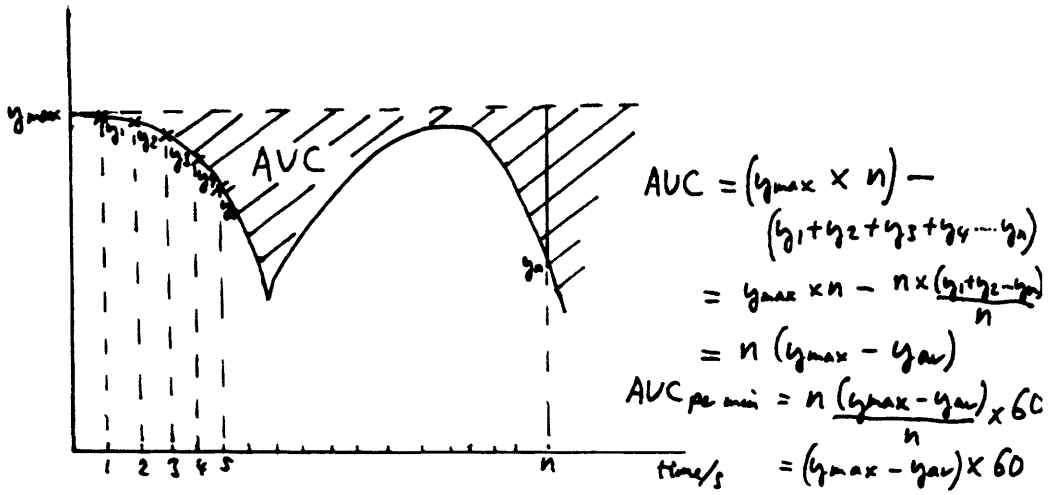
6. Copy file was deleted.

5.4.4 Calculation of area under the curve measures

Data used was the digital output to computer file of TOI or SaO2. Initially a simple plot of TOI over time was examined to ensure there were no gaps or major baseline shift.
For a series of saturation values, summing consecutive values is the same as multiplying the average value by the number of values. We need to sum the difference between the maximum value and each value. Area under the curve was therefore calculated by subtracting mean TOI from maximum TOI and multiplying by the number of seconds (for output every s) (See Figure 27). AUC per minute was then computed by dividing by the number of seconds and multiplying by 60. This calculation was performed for AUC from maximum TOI and then from max – 2, max – 4 and max - 10, restricting the data set to include values up to the specified maximum each time.
TOI max was defined as the lowest value that 99% of recorded values were less than or equal to, so that single outlying values did not have a big effect on the resulting AUC.
Values of SaO_2 <50% and TOI < 40% were assumed to be artifactual (loss of contact) and omitted from analysis.
No attempt was made to distinguish sleep time, sleep stages or apnoea time.

Figure 27. Simple calculation of area under the curve

Ymax = maximum value of y, y1,y2 etc are consecutive points on the y axis, n are consecutive timepoints on the x axis, AUC is area under the curve as shown.



5.5 STATISTICAL METHODS

5.5.1 Introduction and definitions

Statistics is the science of collecting, summarising, presenting and interpreting data, and of using them to estimate the magnitude of associations and test hypotheses (141). Methods of data collection have been described. The data collected in any investigation consists of measurements taken on individuals. The number of individuals is called the sample size. Any aspect of an individual that is measured or recorded is called a variable. Numerical variables may be either continuous or discrete and the statistical methods applied for analysis differ.

The raw data obtained from OSA patients analysed in this thesis falls into two parts. In the first sections the "individuals" were apnoeas and many different variables were measured per apnoea. Particular statistical methods needed to be applied because we used data from more than one apnoea per patient in a combined data set, which resulted in clustering of

the data because of variation between subjects. In the subsequent analysis for the prospective study we obtained single summary readings for each subject and so the "individuals" were different subjects. Statistical analysis in this section is therefore more straightforward.

5.5.2 Discussion of distribution of data including the use of parametric and non-parametric tests

Distribution of data

The appropriateness of a particular statistical test for a set of data depends on both sample size and frequency distribution. The normal distribution is a good empirical description of the distribution of many variables. We are interested in how closely the sample mean approximates the population mean (the generalisability of the results). Even when individual observations are not normally distributed, the sampling distribution of the mean is normal, provided that the sample size is not too small (141). A sample size of 15 or more is generally enough for this assumption. This forms the basis of the calculation of confidence intervals as used in this thesis. Most of the variables were distributed as a normal or skewed normal distribution as shown in Figures 28 and 29. The positively skewed normal distribution is also the typical distribution of measures of sleep apnoea severity in a population for example AHI (142). The exception shown is minimum TOI in Figure 30 where there is substantial variation between subjects resulting in non-normality in the combined dataset resulting in need for statistical techniques to adjust for between subject variation as described below.

Figure 28. Example of distribution of TOIdiff in 1036 apnoeas overlaid with an appropriately scaled normal distribution with same mean and standard deviation as the data.

The data approximates to a normal distribution, however the apnoeas within the positive skew are almost all from a subset of 3 or 4 of the subjects. Analysis of the whole dataset therefore adjusted for this clustering of the data by subject. TOIdiff is change in tissue oxygenation index for each apnoea

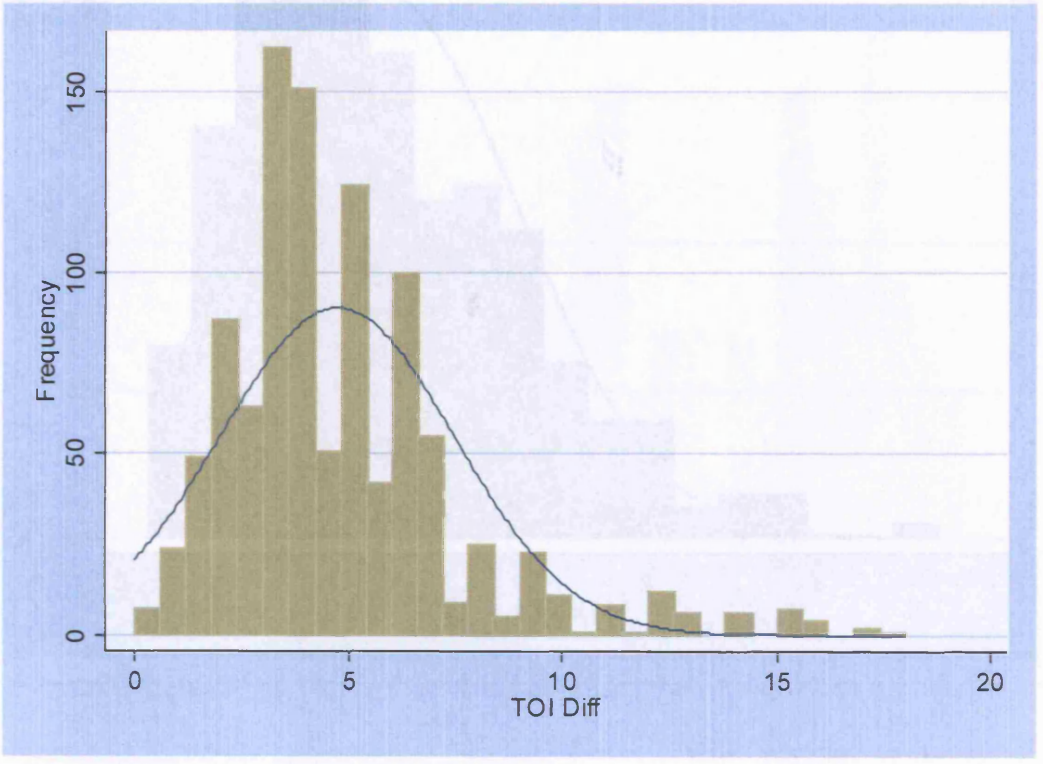


Figure 29. Example of distribution of ctoxdiff in 303 apnoeas overlaid with an appropriately scaled normal distribution with same mean and standard deviation as the data.

The data approximates to a skewed normal distribution. Analysis of the whole dataset adjusted for clustering of the data by subject. Ctoxdiff is change in cytochrome oxidase for each apnoea

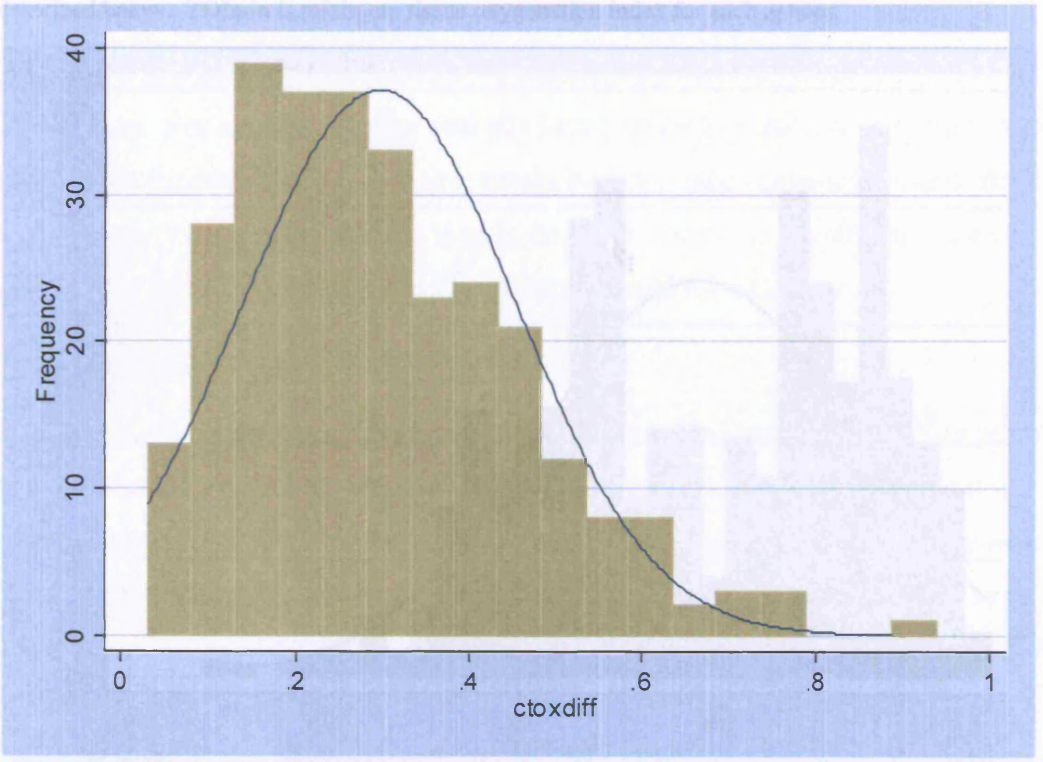
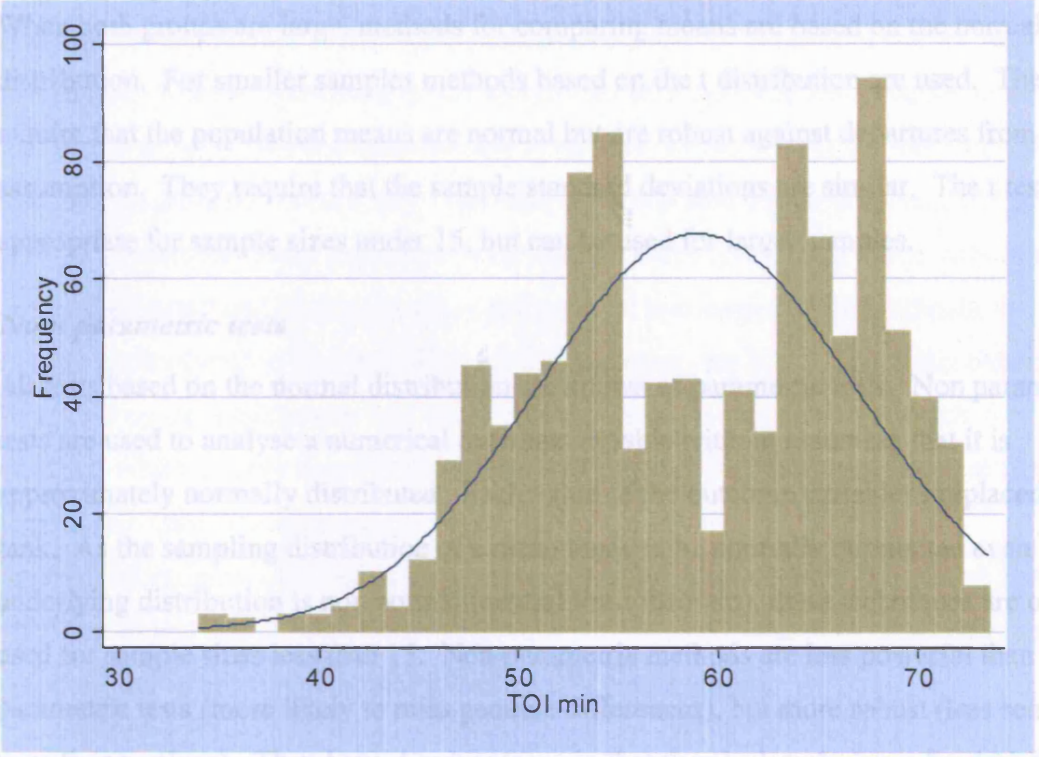


Figure 30. Example of distribution of TOImin in 1036 apnoeas overlaid with an appropriately scaled normal distribution with same mean and standard deviation as the data.

The data in non-normally distributed and appears bimodal because of clustering of absolute TOI values by subject. Analysis of the whole dataset therefore adjusted for between subject variation as described below. TOImin is minimum tissue oxygenation index for each apnoea



Regression and correlation

The strength of the association between two numerical variables is conventionally assessed using regression or correlation. The equation of the regression line for dependent variable y against independent variable x is y = ax +b, where a is the regression coefficient. . The statistical package produces a p value testing the null hypothesis that the regression coefficient is equal to zero.

Two assumptions underline linear regression. The first is that, for any value of x, y is normally distributed. The second is that the magnitude of the scatter of the points about the line is the same throughout the length of the line. For each linear regression a scatter plot is first drawn to ensure the relationship is approximately linear (141). Correlation coefficients examine the strength of the linear association between outcome and exposure variables. Correlation coefficients vary from -1 to +1 and equal zero if the variables are

not associated. The significance of a particular correlation coefficient depends on sample size and can be obtained from tables (eg Biometrika Tables for Statisticians (143)).

Comparison of means.

When both groups are large, methods for comparing means are based on the normal distribution. For smaller samples methods based on the t distribution are used. These require that the population means are normal but are robust against departures from this assumption. They require that the sample standard deviations are similar. The t test is appropriate for sample sizes under 15, but can be used for larger samples.

Non- parametric tests

All tests based on the normal distribution are known as parametric tests. Non parametric tests are used to analyse a numerical outcome variable without assuming that it is approximately normally distributed. Each value of the outcome variable is replaced by its rank. As the sampling distribution of a mean tends to be normally distributed even if the underlying distribution is non normal (central limit theorem), these techniques are only used for sample sizes less than 15. Non-parametric methods are less powerful than parametric tests (more likely to miss genuine differences), but more robust (less sensitive to outlying values). They have disadvantages in that they lack techniques for deriving confidence intervals, they can never produce small p-values if sample sizes are extremely small, and they are not easily extended to situations where it is necessary to take into account the effect of more than one variable on the outcome (141). They were therefore not appropriate in most of the statistical analysis in this thesis. Sample sizes for apnoea analysis were 1036 apnoeas in chapter 7 (15-160 per patient); 303 apnoeas in chapter 8 (29-40 per patient); and 287 apnoeas in chapter 9 (6-59 per patient). In the latter analysis a single patient had less than 15 apnoeas for analysis. In chapter 11 the number of subjects for comparison was 56. Most of the COPD analysis (chapter 13) was comparing changes on multiple observations within subject rather than between subject.

Statistical methods for repeated observations

In our analysis it was necessary to combine repeated apnoeas from single subjects in a single dataset. Because of intrasubject correlation it is misleading to analyse this sort of

data by combining repeated observations from several subjects and then calculating the correlation coefficient as if the data were a simple sample (144). The choice of analysis depends on the question asked. If we want to see if subjects with high values of ΔTOI also tend to have high values of ΔSaO_2, we are interested in whether the average ΔTOI for a subject is related to the subject's average ΔSaO_2. An appropriate test for this comparison would be the correlation between the subject means (145). In our analysis we were more interested in whether increasing ΔTOI within the individual was associated with an increase in Δ SaO_2. We therefore wanted to remove the differences between subjects and look only at changes within (144). We were recommended by the department of statistics at UCL to use a two level regression, with subject at one level. This was achieved using the "xtgee" command of Stata (146) which enabled two level multiple regression, specifying the variable "subject id" to group the data at one level. The initial dataset was examined by the statisticians who confirmed that this analysis was appropriate for the variables which mainly approximated to skewed normal distributions. They confirmed that logarithmic transformation was not required.
Analysis of variance of ΔTOI in this dataset confirmed that 20-30% of variance was between subject and 70-80% was within subject. The contribution of between subject variation was greater for absolute values of TOI than changes.

5.5.3 Calculation of sample size for the studies

Sample size calculations are conventionally carried out prior to commencement of a study comparing two groups of subjects. For our study of neuropsychological function in OSA, the background to which is presented in this thesis, the sample size was calculated to detect a specified difference in neuropsychological outcome. Simple snorers were used as controls in the neuropsychological tests and power calculation was performed assuming patients with OSA and snorers form a continuous distribution of AHI (142). This power calculation indicated that 92 subjects would be required to give a median effect at the 0.05 level. Neuropsychological results are not presented in this thesis but we completed a total of 104 people (59 OSA subjects and 45 snorers).

Most of the analysis involved comparison of two continuous variables in a single group of individuals (apnoeas or subjects), rather than comparison of two groups of individuals.

There are no readily available formulae for sample size calculation in this situation (although tables for calculating significance of the correlation coefficient depend on sample size(143)). A form of sample size calculation can be made by grouping a continuous variable into two groups, below and above the median value, and then considering the mean value of a second variable separately for those two groups. One can then use the formula for comparison of 2 means.

This formula is $\frac{(u + v)^2 (\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$

where u is the one-sided percentage point of the normal distribution corresponding to 100% - the power (u = 1.28 for a power of 90%); v is the percentage point of the normal distribution corresponding to the (two sided) significance level (v = 1.96 for a significance level of 5%), $\mu_1 - \mu_0$ is the difference between the means and σ_1, σ_0 are the standard deviations of each group (141).

Sample size calculations for the dataset from validation study 1

Using the relationship between ΔTOI and Δ SaO_2 and the current dataset as no other similar data was available at the time, the median ΔTOI was calculated for each subject. Δ SaO_2 was grouped into two equal groups for ΔTOI above and below the median value and mean Δ SaO_2 and standard deviation of these two groups were obtained. The standard deviations thus obtained were entered into the equation with a value of difference between means of 4% which was thought to be a clinically significant difference. This then gave sample size values for the different subjects as follows (see Table 6), and a mean required sample size of 22.6 for power of 90% and significance of 5%. Actual analysis will obtain greater power by considering exposure quantitatively, but lose some by controlling for confounding.

Table 6. Calculated and actual sample sizes for 13 subjects in first validation study

Sample sizes calculated by grouping ΔTOI in two groups about the median and calculating mean and standard deviation for Δ SaO_2 in each of these groups according to the formula for sample size calculation for comparison of two means as given above (141). Sample size is calculated to detect a difference of 4% SaO_2 with significance level 0.05 and power of 90%. Sample sizes vary for different subjects because of variation in standard deviations in SaO_2 in different subjects.

Subject id	Calculated sample size	Actual sample size
1	29	130
2	45	160
3	9	48
4	20	90
5	81	17
6	49	110
7	3	15
8	10	27
9	5	32
10	8	71
13	9	108
15	14	125
16	12	103
Mean	22.6	

Calculation of sample size for cytochrome oxidase and CBV calculations

Using an estimated standard deviation for cytox of 0.1μM the above formula gives a required sample size of 5.25 apnoeas per subject for an estimated significant difference between groups of 0.2μM, for power of 90% and significance of 5% and 7.5 apnoeas per subject for significance of 1%.

Using an estimated standard deviation for CBV of 0.1ml/100g the above formula gives a required sample size of 9.3 apnoeas per subject for an estimated significant difference between groups of 0.15 ml/100g, for power of 90% and significance of 5% and 13.3 apnoeas per subject for significance of 1%.

We aimed to study 40 consecutive apnoeas per subject and achieved 40 in 6 subjects, 29 and 32 in the remaining 2 subjects.

Calculation of sample size for cbfv calculations

Using an estimated standard deviation for TOI of 1.2 the above formula gives a required sample size of 7.6 apnoeas per subject for an estimated significant difference between groups of 2% for power of 90% and significance of 5%; and 16.9 apnoeas per subject for significance of 1%. All apnoeas during the study naps were analysed and the number studied in 7 individuals were 6,16, 46, 49, 54, 57, 59, so the minimum sample size was achieved in all but 1 subject.

5.5.4 Correction for multiple comparisons

Even if there is no association between variables one in twenty comparisons will be statistically significant at the 5% level by definition. This is a particular problem when the effect of many different variables on eg ΔTOI are examined, and interpretation of significant findings should be cautious if the analysis has not been guided by an a priori hypothesis. The problem may be avoided if only comparisons specified in the hypothesis are examined. If data are subjected to "dredging" where all possible variables are compared, there is a risk that comparisons which arose by chance are reported as significant (141). Where the hypothesis involves multiple factors, a higher threshold for significance of eg 0.01 is recommended.

There are some statistical techniques to minimise the chance of this happening, for example the Newman-Keuls procedure based on the distribution of the studentised range and the Scheffe procedure which indicates significance much less readily than the t-test (147). We performed 3 comparisons for the dataset in chapter 7, 3 for the cytochrome data, 3 for CBV data, 7 in chapter 9, and 4 in the COPD analysis (chapter 13). All comparisons made were reported and so there is no misleading selective reporting. We did not feel that correction for multiple comparisons was indicated in these analyses. Correction for multiple comparisons could be applied to the data in chapter 11 where multiple possible TOI summary measures are compared with similarly derived saturation variables and with conventional polysomnography variables. However all measures of sleep apnoea severity are heavily intercorrelated and so the interpretation applied to

significant p values is minimal. In fact the results in this chapter where no correlation occurs are the more interesting.

5.5.5 Other methods of comparing data in validation studies

The studies reported are called validation studies, but are not true validation studies in the conventional sense of the description. A validation study should compare a new way of measuring a variable with the accepted way of measuring it. The new and old methods should produce similar absolute values – it is not enough that they correlate. There are specific statistical techniques for this situation as described below. As there is no accepted way of measuring cerebral tissue oxygenation, TOI cannot be validated in this way. It can only be validated indirectly, by showing what factors affect it. Our analyses showed that, for example, CBFV and Δ SaO_2 changes correlated with TOI changes, but were measured in different units in the case of CBFV and would not be predicted to be identical in the case of Δ SaO_2. The methods for assessing agreement between two methods of clinical measurement are therefore not appropriate to the TOI validation studies reported here. These methods include the Bland-Altman plot where the difference between the two methods of measurement is plotted against their mean (148). An alternative method where a gold standard is available is to plot Receiver Operating Characteristic curves. This would be appropriate if a particular TOI cut off was used to diagnose a clinical condition or a significant degree of cerebral hypoxia measured by another technique with an already validated cut-off. Two by two tables of true and false positive and negatives at different TOI cut-offs can be combined in a graph of specificity against sensitivity to see which TOI cut off has maximum sensitivity and specificity in relation to the accepted technique. This plot is know as the receiver operating characteristic curve and is very useful in validation of diagnostic tests (147).

5.6 RELIABILITY AND REPEATABILITY OF MEASUREMENTS

5.6.1 Blinding and bias in techniques of analysis used

Statistical methods provide techniques for describing the effects of random error in analysis, bias is systematic error and can be minimised by study design. Bias is defined in Last's Dictionary of Epidemiology as any trend in the collection, analysis, interpretation or publication or review of data that can lead to conclusions that are systematically different from the truth. In a randomised control trial it is very important that the people making the observations are blind to the outcome and treatment allocation of the study. If they are not there is a potential source of bias in the study. In the neuropsychological study the neuropsychologists were blind to the diagnosis (OSA or simple snorer) and also to any polysomnography results. The polysomnography scorers were blind to the neuropsychological results. There two datasets were not combined, and no analysis was performed until all study visits had been completed. Bias introduced by the observer making the measurements in a study may be non-random, because the observer (deliberately or unknowingly) systematically selects data to obtain a positive result. Observer bias may be minimised by blinding observers to the hypothesis under consideration (less of an issue in a predominantly observational study), training observers and use of standard protocols, or replacing human judgement by automated procedure.

5.6.2 Manual vs automated scoring of eg respiratory events, and implications for observer bias

Polysomnography scoring was performed by 4 operators using the Compumedics® automated analysis, manually checked.according to a standardized sheet of staging and event scoring criteria according to accepted definitions in 1998. Repeated scoring by a single or different operators was not performed because of time constraints. Sleep staging and manual event scoring in the studies was peripheral to the main analysis, and therefore

unlikely to be a source of bias. TOI scoring for chapter 7 was perfomed by AV and AM, for chapter 8 by AM alone, and for chapter 9 by AM, with a separate analysis on the same dataset carried out by P A-R.

All TOI scoring in the validation studies was performed manually, as no automated option was available. Identification of events was automated using the Compumedics® software in chapter 7, and manual according to a predefined definition in chapters 8 and 9. These definitions were a TOI drop of 2 lasting 4s or more in a run of 2 or more for chapter 8, and cessation of airflow for 10s from the capnogram trace for chapter 9. Manual reading off of values from the traces was performed on the compumedics® software for chapter 7 and in Excel® for chapters 8 and 9. In all cases the cursor was placed over the trace and the maximum or minimum visually identified was read off. Several adjacent points were clicked on to check that the correct maximum had been identified. As values were read off and not measured, all recorded values must have been part of the trace, and there was little possibility of systematically over-estimating values. Where there were runs of consecutive apnoeas the changes corresponding to each one were more easily defined, and for this reason, subjects with severe sleep apnoea were invited to participate where possible, and the need for consecutive changes formed part of the definition in chapter 8. Detailed manual analysis took many hours for each subject, and for this reason repeated analysis was not undertaken by the same or a different observer. Attempts were made to minimise bias by using strict protocols as above.

Aware of the problems of manual scoring, methods of summarising TOI overnight by AUC or dip rate were developed independent of manual scoring. The AUC calculations used the continuous data set without removing awake time or regions of noise. This minimised potential bias and made the analysis reproducible, but would make our results less likely to detect a true difference. For the dip rate analysis the Compumedics® software was used, entering parameters appropriately for the analysis, and swapping the channel names so that the TOI channel was analysed automatically. Only machine identified events were used, and where the machine flagged up "unsure", and manual checking would usually have been performed, these unsure events were ignored in order to make the analysis entirely reproducible from the protocol listed earlier in chapter 5. Again because of time constraints, no double reporting of studies by different observers was performed.

It is common practice for sleep studies to be either part or entirely manually scored, as this is considered to be more accurate than automated systems because of the complexity of the datasets. It is also common, particularly in oximetry systems, for sections of data that are noisy and therefore probably awake time, to be removed by eye. This is because many of the algorithms for oximetry trace analysis are relatively simple and do not differentiate dips from other saturation variation. Generally manual polysomnography systems are more accurate than automated ones, and are reproducible with protocols and training, but are time-consuming as data is analysed in 20-30s epochs over a full night study (149). Automated systems are more reproducible, less accurate, may not be quicker and are more expensive (150). A combination of an automated poly system with manual checking has been recommended (149) with the proviso that automated analysis should only be performed by those able to perform a visual analysis. For the newer limited sleep studies, manual analysis has been shown to be more accurate when compared to polysomnography than automated analysis software (151). Automated analysis programmes even when provided by the manufacturer may then be inferior to visual analysis because of the multiple simultaneous recordings. The NIRO had not been previously used much in sleep studies and no automated analysis was available. Because of perceived problems with reproducibility because of manual selection of data for analysis in the validation studies, an automated technique without manual correction was used for dip rate analysis in the prospective study, using the software for SaO_2 dip rate analysis. The absence of manual checking meant that some apnoeas labelled as "unsure" were not analysed, so accuracy was traded against reproducibility.

5.6.3 Method of performing reproducibility measures that would have enhanced the validity of the technique.

There are theoretical reasons why baseline TOI varies in the same patient on different occasions. Even pulse oximetry saturation varies from day to day in a subject over a small range. TOI also depends on cerebral blood flow and local oxygen consumption and so will be sensitive to changes in blood pressure and local cerebral activation. Reproducibility of baseline values was therefore not performed in awake subjects on different occasions. Variability of baseline traces was performed using the coefficient of variation, which is the standard deviation of a series of values as a proportion of the mean.

Error in the recordings will arise both from variation in the actual measurements (which is impossible to distinguish from true variation because of the absence of a gold standard) and from error in reading of the measurements by the individual operator. This error can be quantified by having the same data scored by multiple operators or by the same operator on different occasions. A measure of the reproducibility of the set of rules used for data collection can then be obtained. For categoric variables the kappa measure of agreement used. Kappa is defined as the difference between observed and expected agreement expressed as a fraction of the maximum difference (147). This approach could have usefully employed to the classification of events if all potential events could be flagged up and presented to 2 operators for classification as apnoea or non-apnoea. The polysomnography software used for chapter 7 does flag up all potential events and this method of data analysis could have been checked in this way. The raw data used in chapters 8 and 9 provided a continuous data set and an algorithm would need to be derived to flag up potential events, subsequently manually checked by 2 observers. In both cases the necessary algorithm was missing, and so although 2 observers could have picked events for analysis, it would be difficult to define events not picked in the continuous data series to compute this statistic.

Once events were picked, the reproducibility of the values of variables read off the Excel® graphs could also have been computed. As these are continuous variables, the appropriate statistical test is the intra-class correlation coefficient. This is a measure of the correlation between the values obtained by two different observers within the same individual (apnoea). Formulae for its calculation are available (147). Measurement of the intraclass correlation coefficient for variables read off by two different observers would have enhanced the validity of the analysis techniques used, but unfortunately the time required for this was not available (as manual analysis of each dataset took many hours, and no second observer was available on this timescale).

6. SUBJECTS AND PROTOCOLS FOR FIRST VALIDATION STUDY IN OSA SUBJECTS

6.1 OVERALL HYPOTHESIS

Measurement of cerebral oxygenation using near-infra red spectroscopy gives more valid information than measurement of arterial oxygen saturation alone

6.2 SUMMARY

The first validation study was on 16 patients with previously diagnosed moderate or severe OSA measuring cerebral oxygenation using the NIRO 300 during daytime naps with simultaneous full polysomnography. This was performed between June 1999 and March 2000.

The work was performed by myself and Dr Arschang Valipour, Research Associate from Vienna, Austria, under the supervision of Professor S Spiro and Dr H Makker, Department of Thoracic Medicine, University College London Hospitals. Work was carried out in the Sleep Unit at the Middlesex Hospital.

6.2.1 Subjects

16 patients agreed to participate in the study, however the recording was technically unsatisfactory in 3 patients. They were invited to participate if they had moderate or severe sleep apnoea diagnosed on a screening sleep study (Visilab, Stowood Scientific Instruments, Oxford, UK). They were all patients of the Middlesex Hospital sleep clinic, a clinic receiving referrals from GP's, ENT surgeons and other tertiary referrals of subjects

with obstructive sleep apnoea. The first 8 subjects were invited to attend for study during the initial loan of the equipment. These subjects were already established on treatment although at least 2 were known to be non-compliant with treatment (on the basis of their own reports). They were asked to stop treatment for at least 2 nights prior to the study. The remaining 8 subjects were consecutive new diagnoses of moderate or severe OSA who consented to attend for the daytime study, prior to commencement of CPAP treatment. Three of the recordings were technically unsatisfactory. Characteristics of the remaining 13 subjects are given in Tables 7 and 8, with dip rate quoted from preliminary Visilab sleep study.

Table 7. Characteristics of 13 subjects in first validation study

Pat. ID	*Age/yrs*	*Gender*	*BMI kg/m2*	*Ethnicity*
GI 1	55	M	33.4	White other
DP 2	35	M	32.6	Black Asian
DS 3	57	M	31.5	White UK
CM 4	56	M	33.8	Black Asian
VP 5	47	M	35.5	Black Asian
SM 6	39	M	39.1	Black Afrocaribbean
MA 7	59	M	29.4	Black Asian
TD 8	61	M	34.3	White UK
WC 9	39	M	35.0	Black Asian
GD 10	44	M	36.8	Black Afrocaribbean
BD 13	55	F	35.0	White UK
PH 15	33	M	36.6	White UK
DK 16	40	M	47.3	White UK

Table 8. Additional descriptive data for 13 subjects. Haemoglobin measurements were made in the subjects included in the cytochrome oxidase and total haemoglobin analysis

Pat. ID	*ESS*	*Dip rate/ per hour*	*Baseline oxygen saturation /%*	*Baseline Hb g/l*
GI 1	20	42.9	100	13.2
DP 2	20	60.0	100	16.1
DS 3	15	40.0	99	15.3
CM 4	19	88.8	100	13.8
VP 5	10	65.5	100	
SM 6	21	95.3	100	15.4
MA 7	11	38.0	99	
TD 8	11	27.1	100	
WC 9	14	25.6	98	14.9
GD 10	14	73.9	100	16.4
BD 13	15	29.6	97	13.6
PH 15	19	87.1	96	15.4
DK 16	20	91.5	100	14.8

None of the patients had a history of lung disorders, or cerebral or myocardial infarction. Subject 2 was undergoing venesection for polycythaemia, and subject 4 was on treatment for type 2 diabetes and hypertension.

Ethical approval was granted by the relevant ethics committee, and all subjects gave verbal consent. Written consent is not currently accepted policy for the clinical use of medical monitoring instruments.

6.2.2 Protocol

The polysomnography electrodes were connected in a standard manner. The pulse oximeter probe was applied to a finger because of problems with signal stability on the ear lobe.

The NIRS optodes were placed in a black plastic holder and attached to the left forehead using a self-adhesive pad as described in chapter 4.

Care was taken to avoid air sinuses and the temporalis muscle and the optodes were placed on as flat a part of the head as possible. The optodes were bandaged in place using a crepe bandage. Once all the apparatus was attached the outputs were tested and the patient was then allowed to sleep in a darkened room for up to 2 hours.

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7. ANALYSIS OF TOI CHANGES IN ASSOCIATION WITH THE POLYSOMNOGRAPHY TRACE FROM FIRST VALIDATION STUDY

7.1 OVERALL HYPOTHESIS

7.1.1 Measurement of cerebral oxygenation using near-infra red spectroscopy gives additional valid information compared to measurement of arterial oxygen saturation alone.

7.2 HYPOTHESES UNDERLYING ANALYSIS IN THIS CHAPTER

7.2.1 Characteristics of TOI differ from characteristics of arterial oxygen saturation.

7.2.2 TOI changes during apnoeas cannot be predicted from arterial oxygen saturation alone.

7.3 SUMMARY.

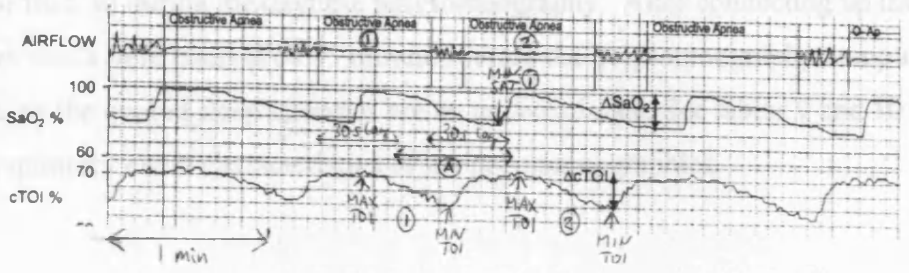
This chapter describes the analysis of the TOI trace and polysomnography trace during daytime sleep for 13 subjects from the first validation study. Results include absolute values of TOI and SaO_2 observed, the relationships between TOI and SaO_2, and other factors affecting the changes in TOI during apnoea including apnoea duration and REM sleep stage. Finally a multiple regression looking at predictors of the amplitude of the TOI dip during apnoea is given.

7.4 DATA ANALYSIS

13 subjects with moderate or severe OSA undertook daytime naps with polysomnography and NIRO monitoring. The TOI channel of the NIRO300 was fed into a spare channel on the polysomnography computer. Analysis was carried out manually using the graphical display and software of the Compumedics® polysomnography system. For each obstructive apnoea/hypopnoea, the lowest SaO_2 value (min. SaO_2), the SaO_2 difference from baseline (ΔSaO_2) and apnoea duration were obtained from the analysis function of the polysomnography software. The computer scans from the end of the apnoea plus a specified time lag (set at 30s for a finger oximeter probe) back to the beginning of the apnoea plus the time lag, to obtain the saturation minimum (see fig 31). The difference between the maximum baseline TOI value preceding each apnoea/hypopnoea and the TOI nadir obtained during each apnoea/hypopnoea related oxygen desaturation was recorded for every event (Δ TOI). This was performed manually using a cursor on the screen.

Figure 31. Figure showing how TOI results were read off the polysomnography trace

This is part of an annotated polysomnography trace with SaO_2 = oxygen saturation by pulse oximetry and cTOI = tissue oxygenation index. Minsat = minimum SaO_2 for that apnoea and maxTOI and minTOI = maximum and minimum TOI for that apnoea. SaO_2 and TOI readings were obtained as follows. For apnoea 1 the polysomnography software scanned from the end of the apnoea plus 30s back to the beginning of the apnoea plus 30s (marked as time period A) on the SaO_2 trace to obtain the minimum saturation 1. Minimum and maximum TOI corresponding to apnoea 1 were identified visually and the cursor was then placed over the point of interest causing a text box to appear which allowed identification of the values max TOI 1 and min TOI 1. This process was repeated for subsequent apnoeas.



All apnoeas for which the recording was technically satisfactory were recorded, so that the total number of events recorded varied from 15 to 160 in different subjects.

7.5 STATISTICAL ANALYSIS

Absolute maximum and minimum values of TOI and SaO_2 were described and compared using scatter plots and regression analysis for the 13 subjects.

Changes in various parameters during each apnoea were described for each subject using mean and standard deviation.

Initial analysis consisted of comparing the TOI and saturation dips in each subject individually. Scatter plots were drawn for each relationship to check they were approximately linear. Linear regression analysis was then used. Acceptable level of significance was taken as $p<0.05$.

Apnoea characteristics in REM and non-REM sleep were compared using a two-tailed t test.

When the data was combined it was necessary to choose an analysis technique suitable for repeated measures, and the xtgee command of stata6 (146) was recommended to us by our statistical advisers at UCL (152). This was a two level analysis where subject identity (id) comprised one of the two levels, and did not provide an R^2 value because of its 2 level

nature. It allowed measurements from repeated apneas in different subjects to be combined in a single analysis. Acceptable level of significance was taken as $p<0.05$.

7.6 POLYSOMNOGRAPHY RESULTS

13 subjects with moderate or severe OSA undertook daytime naps with polysomnography and NIRO monitoring. Recordings were obtained during a mean sleep period of 89.9 min (SD 24.4) with a mean sleep latency of 2.1 min (SD 3.2). Slow wave sleep was observed in eleven of the subjects and rapid eye movement (REM) sleep in four. Eleven subjects had an AHI greater than 30 during the daytime polysomnography. After connecting up the apparatus there was a time interval of <5 minutes before the polysomnography computer was turned on, so the quoted sleep latencies are an underestimate. See tables 9 and 10 for staging and respiratory event characteristics of the polysomnographies.

Table 9. Sleep latency, total sleep time and sleep staging data for 13 subjects.

Pat. ID	*Sleep latency /min*	*Sleep time/min*	*Stage 1 min*	*Stage 2 min*	*Stage 3 min*	*Stage 4 min*	*REM/ min*
GI 1	0	n/a					
DP 2	0	101	5.7	41	48	0.7	5.6
DS 3	7	30	7	23	0.3	0	0
CM 4	0	95	8.7	78	7	0	1.3
VP 5	n/a	120	4	97	12	0	7
SM 6	1.3	77.7	5.3	55.7	6.7	0	10
MA 7	0.7	36.7	10.7	22.7	3.3	0	0
TD 8	n/a	57.3	2.3	44.3	4.3	0	6.4
WC 9	10	18.7	1.3	16.7	0.7	0	0
GD 10	0	89	12	28	27	9	13
BD 11	0.7	76.3	3.3	61.7	5.3	0	6
PH 12	0	80	7	50	22	0	0
DK 13	2	61	6.7	37	16.3	1	0

Table 10. Respiratory analysis from polysomnography in 13 subjects.

All indices are per hour.

Pat. ID	*Apnoea index central*	*Apnoea index obstructive*	*Apnoea index mixed*	*Hypopnoea index*	*AHI*
GI 1	0	58.8	0	9.4	69.8
DP 2	0.6	84.1	5.9	3.6	94.2
DS 3	0	74	0	2	76
CM 4	0	56.5	0	2.5	59
VP 5	8.5	24.4	4	3.5	40.4
SM 6	1.5	75.5	9.9	9.2	96.1
MA 7	0	0	1.6	13	14.6
TD 8	0	5	0	20.9	25.9
WC 9	3.2	37.9	6.3	9.3	56.7
GD 10	0	40.7	0.7	2.7	44.1
BD 11	0	28.3	0.8	55.8	79.7
PH 12	0	55	0	40	95
DK 13	0	39.7	4.8	55.2	99.7

7.7 THE TOI TRACE

Figure 32 gives an example of the polysomnography and TOI trace obtained in one subject (subject 1) during a period of repetitive apnoeas.

Figure 32. Polysomnography trace in subject 1 during OSA

SaO_2 = oxygen saturation, cTOI = tissue oxygenation index, ΔcTOI is the TOI change for that apnoea, ΔSaO_2 is the SaO_2 change for the corresponding apnoea.

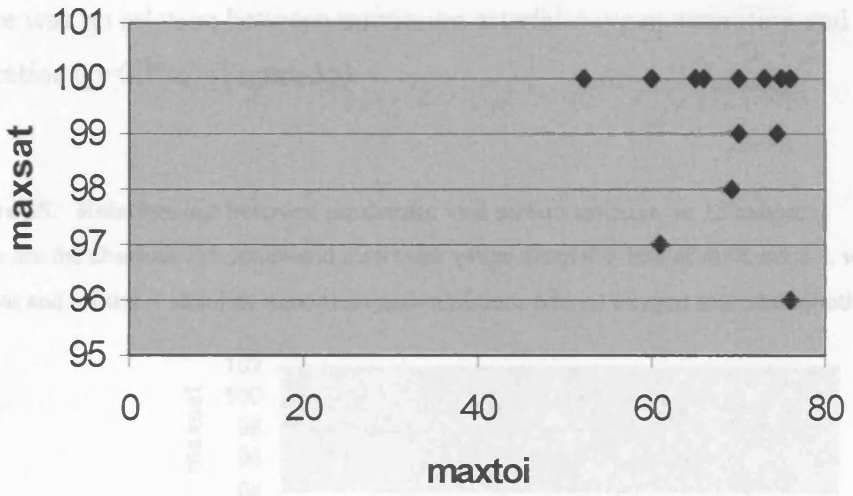
It illustrates that repetitive drops in TOI were observed during successive apnoeas/hypopnoeas. There was a time lag of approximately 20s between the SaO_2 (measured from a pulse oximeter using a finger probe) and TOI dips. The TOI and SaO_2 nadir occurred at 9.5 (± 2.8) sec and 28.7 (± 5.0) sec (range 6.9 - 15.9 vs. 24.7 - 38.7 sec; $p < 0.001$) after the end of an apnoea/hypopnoea.

Baseline TOI varied from 50.2 – 75.0%, where awake baseline SaO_2 was 94% or above in all subjects. No shifts in the TOI baseline were detected during periods of relaxed wakefulness or sleep stage transitions in Non-REM sleep. In 3 subjects the TOI baseline was affected by major body movements. The median coefficient of variation of the TOI immediately preceding each apnoea was 2.4% (range 1.2 to 8.1%) in all subjects; median 2% (range 1.2 to 3.5%) in 10 subjects without baseline shift.

7.7.1 Initial observations on TOI in 13 subjects

There is very limited data on the relationship between TOI and arterial saturation in different subjects, as so much validation work has been performed in neurosurgical patients with SaO_2 fixed. Otherwise fit sleep apnea patients tend to have very similar baseline SaO_2 values (>95%), but variable minimum SaO_2 values depending on apnea duration and other factors. We wondered if the same were true for TOI values. Absolute maximum and minimum TOI and arterial saturation from the dataset obtained from apnoea analysis were compared in 13 subjects. There was more variability in maximum TOI values than maximum saturation values, and no correlation between the two (p=0.6) (Fig 33).

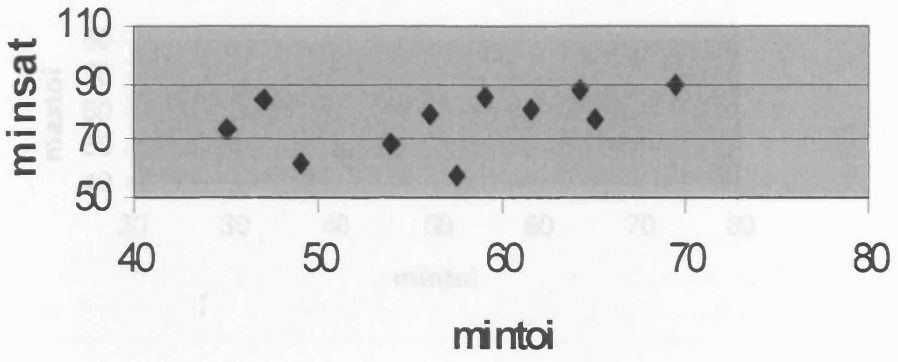
Figure 33. Graph of maximum saturation against maximum TOI in 13 subjects
These are absolute maximum values from the data of each subject, with units % saturation. Maxsat = absolute maximum arterial oxygen saturation, max toi = absolute maximum tissue oxygenation index, both in %



However there was some relation between absolute minimum arterial saturation and TOI, reflecting severity of OSA (Figure 34).

Figure 34. Relationship between absolute minimum SaO_2 and TOI. $R^2 = 0.54$ Coeff = 0.59 p=0.004

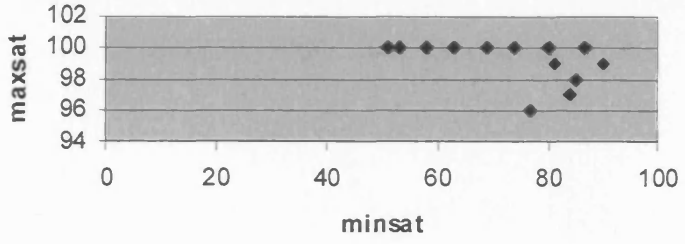
These are absolute minimum values from the data of each subject, with units % saturation. MInsat = absolute minimum arterial oxygen saturation, mintoi = absolute minimum tissue oxygenation index, both in %



There was no relation between maximum arterial oxygen saturation and absolute minimum saturation (p=0.126) (Figure 35).

Figure 35. Relationship between maximum and minimum SaO_2 in 13 subjects.

These are the absolute maximum and minimum values from the data of each subject, with units % saturation. Maxsat and minsat = absolute maximum and minimum arterial oxygen saturation, both in %

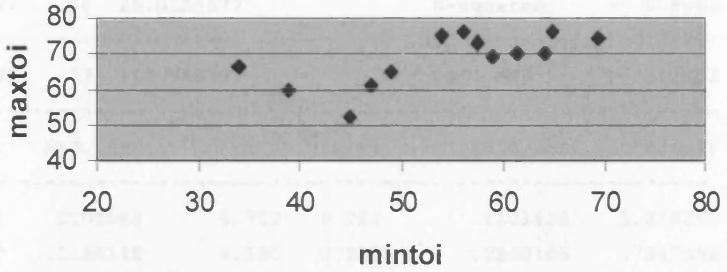


However TOI minimum was related to TOI maximum quite strongly (Figure 36). This suggests that individual factors influence TOI measurements and need to be taken into account when subjects are compared. However TOI is marketed as an absolute saturation

measurement, and the relation between absolute minima TOI and SaO_2 suggest that this is legitimate.

Figure 36. Relationship between maximum and minimum TOI. **R^2=0.47, p=0.01**

These are the absolute maximum and minimum values from the data of each subject, with units % saturation. Maxtoi and mintoi = absolute maximum and minimum tissue oxygenation index, both in %



The main decision to be made when analyzing TOI values was whether to bother with absolute values or whether to stick to measures of change as had always been conventional in previous NIR models, because of the degree of intercorrelation within the TOI values of an individual. In multiple regression both TOI maximum and arterial saturation minimum significantly predict TOI minimum, and together they explain 80% of the variance (Table 11). We proceeded on the basis of these initial observations to look at both TOI dip and TOI minimum in analysis but to use a statistical method that corrected for the fact that observations within an individual were more similar than observations between individuals.

Table 11. Regression analysis showing predictors of minimum TOI during sleep apnoea

This illustrates the statistical output from the program Stata(146). minTOI = absolute minimum TOI, maxTOI = absolute maximum TOI, minsat = absolute minimum SaO_2

```
 regress   mintoi  maxtoi  minsat
  Source |       SS       df       MS                  Number of obs =      13
---------+------------------------------                F(  2,    10) =   20.81
   Model |  1082.53436     2   541.26718                 Prob > F      =  0.0003
Residual |  260.125577    10  26.0125577                 R-squared     =  0.8063
---------+------------------------------                Adj R-squared =  0.7675
   Total |  1342.65994    12  111.888328                 Root MSE      =  5.1003
------------------------------------------------------------------------------
  mintoi |      Coef.   Std. Err.       t     P>|t|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
  maxtoi |   .7792175   .2105048      3.702   0.004       .3101836    1.248251
  minsat |   .4784729   .1150118      4.160   0.002       .2222106    .7347352
    _cons |   -34.3595   14.75388     -2.329   0.042      -67.23318   -1.485812
```

7.7.2 Mean values of SaO_2 and TOI variables during apnoea

Mean values for each patient of SaO_2 and TOI variables during apnoea are shown in Table 12. These values are averages of changes in TOI and SaO_2 and of minimum values for individual apnoeas. The number of apnoeas averaged per patient varied from 15 to 160. Mean minimum saturation varied from 76.7 to 93.8 and mean minimum TOI varied from 47.6 to 70.5. The average change in TOI during apnoea (ΔTOI) varied from 1.4 to 6.9, and in arterial saturation (ΔSaO_2) from 3.8 to 21.8. As discussed above there was a wider variation in baseline TOI than baseline saturation, and so there was a bigger range of mean minimum TOI, despite the changes during apnoea being smaller.

Table 12. Mean values for SaO_2 and TOI variables for 13 patients with OSA during daytime sleep.

SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, ΔTOI = mean TOI change during apnoeas, ΔSaO_2 = mean SaO_2 change during apnoeas, mean minimum TOI = mean of minimum TOI reached during each apnoea, mean minimum SaO_2 = mean of minimum SaO_2 reached during each apnoea, duration = mean apnoea duration.

id	Number of events	ΔTOI/%	ΔSaO_2%	Mean min TOI %	Mean min SaO_2 %	Duration/s
1	130	6.6 (4.4)	14.7 (6.8)	63.1 (4.5)	81.8 (5.9)	30.4 (13.6)
2	160	5.7 (2.6)	21.8 (6.9)	51.7 (3.5)	76.7 (7.1)	25.7 (7.8)
3	48	4.3 (1.5)	12.4 (3.3)	64.0 (1.4)	85.0 (3.0)	32.8 (9.8)
4	90	2.5 (1.1)	10.1 (4.4)	47.6 (1.2)	87.7 (4.4)	25.9 (10.1)
5	17	6.9 (1.9)	11.6 (9.2)	53.9 (3.3)	85.0 (8.8)	33.4 (8.8)
6	110	5.2 (3.1)	17.0 (6.4)	53.0 (7.0)	81.0 (6.8)	19.8 (8.1)
7	15	1.4 (0.6)	3.8 (1.4)	70.5 (1.0)	92.5 (1.4)	15.4 (3.5)
8	27	1.8 (0.7)	4.9 (2.9)	66.2 (1.0)	93.8 (2.7)	20.9 (12.2)
9	32	3.7 (1.8)	8.8 (2.4)	63.5 (2.4)	90.4 (2.2)	17.8 (5.0)
10	71	6.3 (1.7)	10.8 (3.1)	61.8 (2.3)	86.7 (4.5)	27.7 (8.3)
11	108	3.5 (1.3)	6.2 (2.6)	53.0 (2.1)	89.9 (2.4)	14.1 (4.4)
12	125	4.0 (1.3)	7.5 (3.3)	69.1 (1.6)	86.4 (3.5)	17.1 (5.0)
13	103	4.9 (1.4)	9.4 (3.1)	66.3 (2.5)	87.7 (2.9)	20.0 (5.7)

7.7.3 Relationships between parameters in individual subjects

The relationships between pairs of recorded parameters were first examined in individual subjects, using simple regression (Tables 13-15). Because of the problems in combining data between subjects it was important to first establish any relationships that existed in individual subjects.

Table 13. Relation between ΔTOI and ΔSaO_2.

TOI = tissue oxygenation index, SaO_2 = arterial oxygen saturation, ΔTOI and ΔSaO_2 are change in TOI and corresponding change in SaO_2 during each apnoea. Statistical analysis is uses simple regression, coefficient is regression coefficient.

id	coefficient	R squared	p	Number of events
1	0.57	0.78	<0.001	130
2	0.33	0.74	<0.001	160
3	0.38	0.71	<0.001	48
4	0.14	0.30	<0.001	90
5	0.15	0.53	0.001	17
6	0.22	0.20	<0.001	110
7	0.23	0.26	0.05	15
8	0.13	0.29	0.004	27
9	0.52	0.47	<0.001	32
10	0.34	0.39	<0.001	71
11	0.15	0.08	0.002	108
12	0.20	0.24	<0.001	125
13	0.22	0.24	<0.001	103

ΔTOI and Δ SaO_2 were significantly related in all subjects (Table 13), however the regression coefficient varied, ie the change in TOI per unit change in SaO_2 varied between subjects.

Mean minimum TOI was related significantly to mean minimum saturation in 8 out of 13 subjects (Table 14). This did not seem to be just a problem of power as some subjects with over a hundred apnoeas did not have a significant relationship. It is more likely that the contribution of individual factors to TOI measurement varied between individuals.

TOI change was significantly related to apnoea duration in 10 out of 13 subjects (Table 15). The number of apnoeas was small in two out of three subjects where the relationship was non-significant. Clearly arterial desaturation will be greater during longer apnoeas, and so multiple regression was necessary to find out if the effect of apnoea duration on TOI change added anything to the effect of desaturation.

Table 14. Relationship between minimum TOI and minimum SaO_2 during each apnoea

TOI = tissue oxygenation index, SaO_2 = arterial oxygen saturation, minimum TOI and minimum SaO_2 are corresponding minima during each apnoea. Statistical analysis is uses simple regression, coefficient is regression coefficient.

id	coefficient	R squared	p	Number of events
1	0.55	0.51	<0.001	130
2	0.45	0.82	<0.001	160
3	0.37	0.62	<0.001	48
4	0.12	0.20	<0.001	90
5	0.29	0.59	<0.001	17
6	0.57	0.30	<0.001	110
7			0.087	15
8			0.068	27
9	0.72	0.43	<0.001	32
10			0.35	71
11			0.68	108
12			0.08	125
13	0.47	0.30	<0.001	103

Table 15. Relationship between ΔTOI and apnoea duration

TOI = tissue oxygenation index, ΔTOI is the change in TOI during each apnoea, here compared to corresponding apnoea duration. Statistical analysis is uses simple regression, coefficient is regression coefficient.

Id	coefficient	R squared	p	Number of events
1	0.27	0.70	0.000	130
2	0.24	0.53	0.000	160
3	0.11	0.51	0.000	48
4	0.53	0.25	0.000	90
5	0.13	0.37	0.009	17
6	0.30	0.60	0.000	110
7	0.04	0.04	0.451	15
8	0.02	0.13	0.062	27
9	0.28	0.57	0.000	32
10	0.07	0.13	0.002	71
11	0.08	0.08	0.004	108
12	0.07	0.08	0.002	125
13	0.03	0.02	0.198	103

7.7.4 Effect of REM sleep stage

Four subjects had apnoeic episodes during REM sleep during daytime naps, and apnoea characteristics were compared in REM and non-REM sleep in these subjects using a 2-tailed t test (Tables 16-19). Changes in TOI, SaO_2 and apnoea duration during REM sleep were significantly greater than in Non-REM sleep in 3 of the 4 subjects. The fourth subject had mean minimum saturations of around 90% both in REM and non-REM sleep and these values were much higher than the other subjects who had REM sleep during the daytime naps, however it is not clear why differences in REM and non-REM sleep were not observed.

Table 16. Differences in parameters in REM and nonREM sleep in Subject 1

REM = rapid eye movement, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, ΔSaO_2 = change in SaO_2 during apnoea, min SaO_2 = minimum SaO_2 during apnoea, duration = apnoea duration, min TOI = minimum TOI during apnoea, ΔTOI = change in TOI during apnoea.

	REM	Non-REM	p
observations	14	116	
Mean ΔSaO_2(%)	24.4	13.6	0.000
Mean min SaO2 (%)	73.6	82.8	0.000
Mean duration (s)	49	28.2	0.000
Mean min TOI (%)	57.6	63.7	0.000
Mean ΔTOI (%)	13.9	5.7	0.000

Table 17. Differences in parameters in REM and nonREM sleep in Subject 2.

REM = rapid eye movement, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, Δ SaO_2 = change in SaO_2 during apnoea, min SaO_2 = minimum SaO_2 during apnoea, duration = apnoea duration, min TOI = minimum TOI during apnoea, ΔTOI = change in TOI during apnoea.

	REM	Non-REM	P
observations	10	150	
Mean Δ SaO_2 (%)	38.6	20.7	0.000
Mean min SaO2(%)	59.3	77.9	0.000
Mean duration (s)	41.3	24.6	0.000
Mean min TOI (%)	40.9	52.4	0.000
Mean ΔTOI (%)	13.2	5.2	0.000

Table 18. Differences in parameters in REM and nonREM sleep in Subject 6.

REM = rapid eye movement, SaO2 = arterial oxygen saturation, TOI = tissue oxygenation index, ΔSaO2 = change in SaO2 during apnoea, min SaO2 = minimum SaO2 during apnoea, duration = apnoea duration, min TOI = minimum TOI during apnoea, ΔTOI = change in TOI during apnoea.

	REM	Non-REM	p
observations	12	98	
Mean Δ SaO_2 (%)	21.7	16.4	0.007
Mean min SaO2 (%)	74.8	81.7	0.001
Mean duration(s)	33.3	18.2	0.000
Mean min TOI (%)	41.0	54.5	0.000
Mean ΔTOI (%)	10.2	4.6	0.000

Table 19. Differences in parameters in REM and nonREM sleep in Subject 13.

REM = rapid eye movement, SaO2 = arterial oxygen saturation, TOI = tissue oxygenation index, ΔSaO2 = change in SaO2 during apnoea, min SaO2 = minimum SaO2 during apnoea, duration = apnoea duration, min TOI = minimum TOI during apnoea, ΔTOI = change in TOI during apnoea.

	REM	Non-REM	p
observations	11	97	
Mean Δ SaO_2 (%)	5.64	6.30	0.43
Mean Min SaO_2(%)	90.2	89.9	0.66
Mean duration (s)	13.5	14.2	0.63
Mean min TOI (%)	53.7	52.9	0.27
Mean ΔTOI (%)	3.65	3.43	0.61

7.7.5 Combined analysis of 1036 apnoeas/hypopnoeas

We had shown that change in SaO_2, apnoea duration and REM sleep stage affect the size of the TOI drop during apnoea in most subjects, however changes in SaO_2 are increased in long apnoeas and during REM sleep, so it was still not clear whether the TOI measurement provided additional information to pulse oximetry. We therefore used regression analysis to see whether the effects of apnoea duration and REM sleep were independent of SaO_2. In a two level regression analysis including all apnoeas the following factors were significantly associated with the magnitude of the fall in cerebral oxygen saturation associated with an apnoea, corrected for interpatient differences: min SaO_2, SaO_2 difference, apnoea duration and REM sleep stage (Table 20). The minimum TOI reached during an apnoea was significantly predicted by min SaO_2 and REM sleep stage, with apnoea duration being borderline significant.

Table 20. Factors affecting apnoea-associated TOI drops and TOI minimum. Two level regression analysis, adjusting for interpatient differences.

CI = confidence intervals, REM = rapid eye movement, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, Δ SaO_2 = change in SaO_2 during apnoea, min SaO_2 = minimum SaO_2 during apnoea, TOI minimum = minimum TOI during apnoea, ΔTOI = change in TOI during apnoea. Statistical analysis was performed using the xtgee command of stata6 (146).

	Factors affecting ΔTOI			Factors affecting TOI minimum		
Factor	Regression Coefficient	95% CI*	p	Regression coefficient	95% CI*	p
ΔSaO_2	0.105	0.023 - 0.187	0.012	0.069	-0.224 - 0.361	0.644
Minimum SaO_2	-0.107	-0.128 - 0.086	0.000	0.328	0.046 - 0.611	0.023
Apnoea Duration	0.092	0.036 - 0.149	0.001	-0.090	-0.180 - 0.001	0.052
REM sleep	2.405	1.134 - 3.676	0.000	-3.970	-7.828 - 0.112	0.044

7.7.6 Conclusions

7.7.7 Characteristics of TOI differ from characteristics of arterial oxygen saturation.

In this chapter we have looked at the initial findings when TOI changes were compared to saturation changes during obstructive sleep apnoea. At the time when we performed this work there was very little data on baseline TOI values in human subjects. We started by looking at maximum and minimum values of TOI and arterial saturation. We were not surprised to find baseline SaO_2 values all between 95 and 100% in otherwise well subjects with OSA. However the baseline TOI values were lower and more variable than SaO_2 values as they depended on the relative proportion of arterial and venous blood under the probe. There was no correlation between SaO_2 and TOI maximum values which is perhaps as expected given that maximum SaO_2 is relatively fixed. There is a correlation between the minimum TOI and SaO_2 values, suggesting that severe apnoea is associated with bigger

changes in both SaO_2 and TOI. Minimum SaO_2 does not correlate with baseline maximum SaO_2, suggesting that minimum saturation is dependent on other factors. There is however a close correlation between an individual's maximum and minimum TOI suggesting that individual factors have a greater influence on TOI values than SaO_2. This description of the characteristics of TOI compared to SaO_2 is important so that more complicated analysis of TOI can be performed and interpreted correctly.

7.7.8 TOI changes during apnoeas cannot be predicted from arterial oxygen saturation alone.

The other important fact established by this early analysis was that TOI changes did occur during apnoea and could not be predicted by arterial saturation changes alone. It has been postulated that cerebral autoregulation might keep cerebral oxygenation constant during peripheral desaturation, and demonstration of any TOI changes during OSA show that this is not the case. Additionally it has also been suggested that any changes in cerebral saturation during apnoea may occur secondary to SaO_2 changes, so that TOI changes can be predicted from and add nothing to SaO_2 changes. Again our results demonstrate that this is not the case and that TOI changes also depend on sleep stage and apnoea duration independently of SaO_2. Cerebral oxygenation will also be affected by cerebral blood flow changes which are greater in REM sleep. We moved on to attempt to characterise the changes in cerebral oxygenation occurring during OSA more fully in later validation studies. We were able to look at total haemoglobin and cytochrome oxidase oxidation state from the NIRO output and this is described in chapter 8, as well as simultaneous CBFV measurement summarised in chapter 9.

8. ANALYSIS OF CYTOCHROME OXIDASE, CEREBRAL BLOOD VOLUME AND TOI CHANGES FROM VALIDATION STUDY 1.

8.1 OVERALL HYPOTHESIS

8.1.1 Measurement of cerebral oxygenation using near-infra red spectroscopy gives additional valid information compared to measurement of arterial oxygen saturation alone

8.2 HYPOTHESES UNDERLYING ANALYSIS IN THIS CHAPTER

8.2.1 Changes in intracellular redox state measured using cytochrome oxidase redox state are seen during obstructive sleep apnoea.

8.2.2 There is a fixed temporal relationship between changes in total haemoglobin and measures of oxygenated haemoglobin during obstructive sleep apnoea

8.3 INTRODUCTION.

The NIRO300 measures cerebral tissue saturation (TOI) using spatially resolved spectroscopy but also gives the basis chromophore concentration changes: OHb, HHb and

cytochrome oxidase. Before tissue saturation measurements were available, chromophore concentration changes used to be extensively analysed to give as much information as possible. The most used haemoglobin derivatives were the Hb difference (OHb – HHb) which gives an idea of the redox state of the haemoglobin and has been superceded by TOI, and total haemoglobin (OHb + THb) a value which can be equated to relative blood volume, and gives limited information about whole blood movement within the tissue. Changes in total haemoglobin occurring during apnoea were observed previously by Hayakawa (Hayakawa) and used to support the view that cerebral blood flow changes do not completely compensate for arterial hypoxaemia during apnoea. In their paper they only illustrated data from one patient, and did not suggest that the temporal relationship of the changes differed between patients. Clearly if the degree of compensation differs between patients this supports our basic hypothesis that the measurement of cerebral oxygenation directly will give more information than measuring arterial saturation alone. We approached this question by looking at total haemoglobin changes in relation to changes in the basic chromophores during individual apnoeas.

Changes in concentration of oxidized cytochrome oxidase can also be calculated to look at intracellular redox state. When the NIRO300 is used clinically the chromophore readings are often ignored and TOI used alone. There are various reasons for this; TOI is an absolute saturation measurement and has been validated as independent of extracranial contamination, unlike the simple chromophore measurements. We chose however to spend some time analyzing total haemoglobin and cytochrome oxidase changes in OSA because of the additional haemodynamic and metabolic information available, and then comparing these changes to cerebral saturation changes measured with TOI.

This chapter presents findings relating to changes in cytochrome oxidase and cerebral blood volume occurring during OSA measured by NIRS in the first validation study in which 13 subjects underwent polysomnography and simultaneous cerebral oxygenation monitoring using the NIRO300 during daytime naps. Changes in cytochrome oxidase and cerebral blood volume were quantified and then correlated to changes in TOI, and TOI dip duration. The temporal relationship between changes in these parameters was examined using cumulative averaging. An attempt was made to explain two different observed temporal patterns.

8.4 DATA ANALYSIS

8.4.1 Subject selection

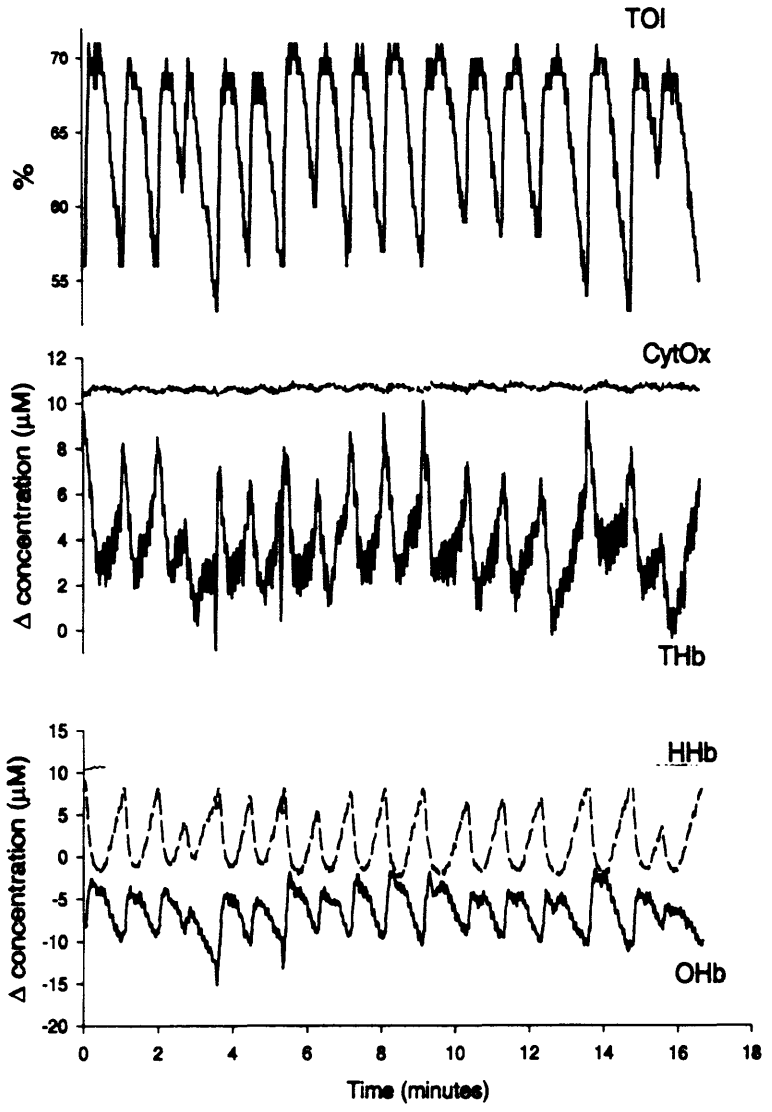
Of the 13 subjects included in analysis of polysomnography traces (chapter 7), five were eliminated from further analysis because their recordings were technically poor, or because they did not have sufficient runs of consecutive apnoeas during the recording period. The five eliminated were subjects 4,5,7,8 and 9. Analysis of cytochrome oxidase and CBV changes was carried out on the 8 patients who had several runs of at least 3 consecutive apnoeas during these daytime naps and were the most severe among the group (subjects 1,2,3,6,10,11,12,13). Three subjects did not sleep during the daytime recording period and were not included in either analysis.

8.4.2 Quantification

Fig 37 shows an example of the raw data from one patient during a run of consecutive apnoeas illustrated graphically. It can be seen that there are repetitive changes in TOI, OHb, HHb, total HB and cytochrome oxidase occurring during apnoeas.

Figure 37. Raw NIRO data from one subject (subject 1) during repetitive apnoeas

TOI = tissue oxygenation index, Cytox = cytochrome oxidase, OHb = oxygenated haemoglobin, HHb = deoxygenated haemoglobin, THb = total haemoglobin (OHb + HHb), all chromophores measured in μM from arbitrary baseline, TOI measured in %saturation.



This raw data did not include SaO_2 or airflow so a standard method of defining apnoea was not available to us. We instead chose to use a prespecified definition of TOI dip and look at the relationship of CBV change and cytox change with this. TOI dips were selected as being >= 2% and >= 4sec, in runs of at least 2 consecutive dips. In the validation paper for the TOI and NIRO300 (80) after accounting for baseline variation in TOI, a ΔTOI of >2% was considered significant, and our previous work using the analogue output of TOI to the

polysomnography system has shown consistent TOI dips occurring in association with apnoeas with a correlation coefficient of 0.94 between 2% dip rate and AHI. The first 40 successive TOI dips fitting the prespecified criteria were selected for each patient (303 dips in total) and maximum and minimum TOI were recorded. For each selected TOI dip the maximum and minimum values of cytochrome oxidase and total haemoglobin occurring during the TOI dip were recorded, as well as the times at which these occurred. The method by which this was done is explained more fully in chapter 5. The duration of the TOI dip from preceding maximum to end minimum was also recorded. Mean TOI dip duration in session 1 correlated with mean apnoea duration from the polysomnography (c=0.94). An adjustment of the NIRS Hb and cytochrome oxidase output is required in order to calculate concentrations and this differential pathlength factor was assumed to be 6.26 in all analysis (96). Cerebral blood volume was calculated from total haemoglobin, using corrections for cerebral large to small vessel haematocrit ratio, cerebral tissue density and subject haemoglobin concentration as previously described (93). We assumed that CBV change was related to change in cerebral blood flow and as such might be a determinant of cerebral oxygenation measured as TOI, that changes in cerebral saturation might affect cytochrome oxidase oxidation state, and that TOI dip duration could be used as a measure of apnoea duration in the absence of a better alternative. The following relationships within an apnoea were therefore studied using linear regression: the effect of CBV change on TOI, the effect of TOI change and CBV change on cytochrome oxidase change, and the effect of TOI dip duration on both cytochrome oxidase and CBV changes. This analysis was carried out initially in each subject separately and then two level multiple regression was used to combine the results to correct for intersubject differences (152).

8.4.3 Cumulative average of changes

Visual inspection of the data revealed two different time relationships between THb changes and TOI changes. To illustrate these two relationships the longest run of consecutive apnoeas of similar length was selected for each of the two patterns. The length of this run happened to number thirteen apnoeas. A cumulative average of OHb, HHb, THb, cytox and TOI was calculated over 13 apnoeas. The method is described fully in chapter 5. Graphs were plotted to illustrate average changes during apnoea for these 2 patterns.

8.4.4 Redox changes in Hb oxidation during CBV increase (OHb ratio)

Total haemoglobin is the sum of OHb and HHb. There is a fixed relation between THb change and CBV change. Whether or not a particular apnoea was of one pattern or the other depended on the relative changes in OHb and HHb during the CBV increase. The change in OHb which occurred during the rise in total haemoglobin was calculated from the OHb values at the minimum and maximum of the THb change for each of the 303 apnoeas. This was signed to distinguish between a rise and fall of OHb and expressed as a fraction of the THb rise (OHbratio). Cerebral oxygenation would increase when total haemoglobin increased if the increase was mainly due to oxygenated haemoglobin. Cerebral oxygenation would decrease when total Hb increased if the increase in THb was mainly due to deoxygenated haemoglobin.
The OHbratio gives an estimate of the redox change during the THb change, and is a useful measurement if THb change is used as a proxy for CBV change to give some idea of the oxygenation of the incoming blood.

8.4.5 Statistics

Baseline variation of the cytochrome signal was described using standard deviation. As the trace starts from an arbitrary zero, coefficient of variation could not be used.
Changes were quantified using mean and standard deviation.
Changes were compared in individual subjects using scatter plots with simple regression analysis. Changes in different subjects were combined using a two level multiple regression, with subject id at one level as described previously.
Confidence intervals were calculated for each point of each parameter of the cumulative averages, but are not presented graphically here.
Acceptable level of significance was taken as $p<0.05$.

8.5 RESULTS

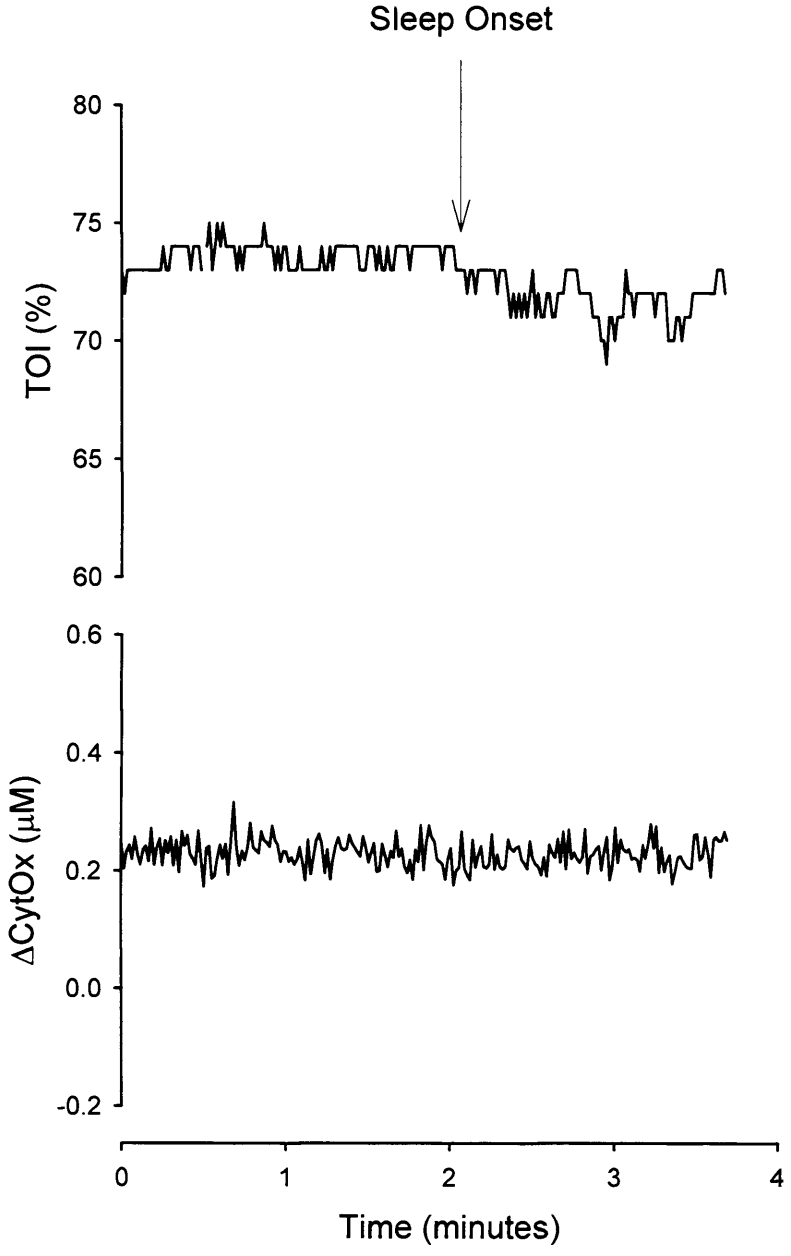
8.5.1 Baseline variables

We looked first of all at the baseline variability in the cytox trace. Figure 38 shows an example of baseline variability in the TOI and cytochrome oxidase traces at sleep onset in

subject 1. Median baseline TOI was 70.5, (range 58 – 78) for the 8 selected subjects in session 1. The median standard deviation of the cytox signal during 2 minutes (120 observations) of non-obstructed breathing in 6 subjects was 0.034 μM (range 0.023 to 0.055). The median cytox standard deviation over a similar period in the 5 subjects without significant OSA was 0.034 μM (range 0.020 to 0.053).

Figure 38. Baseline variability at sleep onset

TOI = tissue oxygenation index measured in % saturation, Δcytox = change in cytochrome oxidase in μM from arbitrary baseline.



8.5.2 Quantification of cytox changes

We wanted to look at how big the changes in oxidised cytochrome oxidase were during apnea, to see if they were physiologically relevant. Quantification of cytochrome oxidase changes ranged from mean (±SD) 0.48 ± 0.08 to 0.13 ± 0.05μM in the 8 patients (see table 21), where absolute cytochrome oxidase concentration in adult brain is <5.5μM (153).

Table 21. Mean changes in cytochrome oxidase redox state during apnoea for 8 patients (29- 40 apnoeas/patient).

TOI = tissue oxygenation index, cytox = cytochrome oxidase, changes are during apnoea defined as TOI dip. Patients are numbered in order of mean TOI change, with ID number from validation study 1 in brackets.

Patient	Mean TOI change +/- SD %	Mean cytox change +/- SD (μM)
1 (1)	12.22 +/- 4.09	0.48 +/- 0.08
2 (6)	7.76 +/- 2.82	0.28 +/- 0.13
3 (2)	6.93 +/- 3.14	0.40 +/- 0.16
4 (10)	5.48 +/- 2.03	0.23 +/- 0.11
5 (12)	5.43 +/- 1.62	0.23 +/- 0.10
6 (13)	5.30 +/- 0.99	0.29 +/- 0.08
7 (11)	4.33 +/- 1.07	0.13 +/- 0.05
8 (3)	4.05 +/- 0.85	0.29 +/- 0.06

8.5.3 Quantitative correlations of cytox changes

We also examined how cytox changes were related to TOI changes, to see if cerebral tissue oxygenation changes were related to intracellular redox state. We considered that if the small changes in ctox correlated with TOI changes they were more likely to be real. Correlations between cytox changes and TOI changes in individual subjects are shown in Table 22.

Table 22. Regression analysis between TOI parameters during apnoea and changes in cytochrome oxidase redox state during apnoea, for individual subjects.

TOI = tissue oxygenation index, cytox = cytochrome oxidase, ΔTOI and Δcytox are changes in TOI and cytox during apnoea defined as TOI dip, duration is duration of TOI dip, coeff is regression coefficient from simple linear regression.

id	ΔTOI/Δcytox			TOI minimum/Δcytox			Duration/Δcytox		
	coeff	r^2	p	coeff	r^2	p	coeff	r^2	P
1	16.96	0.13	0.04	-14.96	0.15	0.03	52.43	0.18	0.02
2	6.66	0.11	0.08	-17.81	0.14	0.05	17.35	0.08	0.12
3	6.90	0.14	0.01	-9.40	0.14	0.01	18.44	0.07	0.08
4	10.06	0.31	0.00	-10.20	0.14	0.02	94.33	0.36	0.00
5	1.45	0.01	0.56	-0.86	0.00	0.67	-1.81	0.00	0.87
6	2.87	0.06	0.13	-5.03	0.21	0.00	-4.85	0.01	0.63
7	5.27	0.07	0.1	-4.43	0.02	0.44	0.14	0.00	0.99
8	5.52	0.18	0.01	-6.77	0.18	0.01	59.51	0.1	0.04

The change in cytochrome oxidase oxidation during apnoea was significantly related to ΔTOI in half the subjects, to TOI minimum in 6 out of 8 subjects and to dip duration in 3 out of 8 subjects. Significant correlations were seen between the magnitude of cytochrome oxidase change and TOI difference, minimum TOI and duration of TOI drop in the group of 303 apnoeas corrected for interpatient differences (Table 23).

Table 23. Two level multiple regression for effects on cytox difference.

TOI = tissue oxygenation index, cytox = cytochrome oxidase, ΔTOI and Δcytox are changes in TOI and cytox during apnoea defined as TOI dip, TOImin is minimum TOI during apnoea, duration is duration of TOI dip. Coeff = regression coefficient. Regression was performed using the xtgee command of stata6 (146).

Effect	Coeff	95% CI	p
TOI min on Δcytox	-0.010	-0.013, -0.006	<0.001
ΔTOI on Δcytox	0.016	0.010, 0.022	<0.001
Duration on Δcytox	0.003	0.002, 0.004	<0.001

8.5.4 Quantification of CBV

We looked at the size of cerebral blood volume shifts during apnoea, and compared them to measured absolute cerebral blood volume from previous NIRS studies. Quantification of changes in CBV during apnoea showed mean (± SD) CBV changes ranging from 0.41 ± 0.13 to 0.09 ± 0.07 ml/100g in the 8 patients (see table 24). The value of absolute blood volume in the normal adult brain using NIRS techniques ranges from 1.1 – 2.85 ml/100g (154, 155), so at most this would equate to a shift of about a third of the blood volume.

Table 24. Mean changes in CBV during apnoea for 8 patients (29- 40 apnoeas/patient).
TOI = tissue oxygenation index, CBV = cerebral blood volume, changes are during apnoea defined as TOI dip. Patients are numbered in order of mean TOI change, with ID number from validation study 1 in brackets.

Patient	Mean TOI change +/- SD (%)	Mean CBV change +/- SD (ml/100g)
1 (1)	12.22 +/- 4.09	0.41 +/- 0.13
2 (6)	7.76 +/- 2.82	0.21 +/- 0.10
3 (2)	6.93 +/- 3.14	0.18 +/- 0.09
4 (10)	5.48 +/- 2.03	0.27 +/- 0.22
5 (12)	5.43 +/- 1.62	0.11 +/- 0.05
6 (13)	5.30 +/- 0.99	0.10 +/- 0.06
7 (11)	4.33 +/- 1.07	0.09 +/- 0.07
8 (3)	4.05 +/- 0.85	0.16 +/- 0.04

8.5.5 Quantitative correlations of CBV changes.

CBV changes can be used as a proxy for cerebral blood flow changes under some conditions. We looked at how cerebral blood volume changes were related to cerebral oxygenation measured as TOI as it would be predicted that changes in cerebral blood volume would affect cerebral oxygenation. We were also interested in whether CBV changes were affected by apnoea duration. The following table shows CBV correlations with TOI changes during each apnoea for individual subjects (Table 25).

Table 25. Regression analysis between change in cerebral blood volume during apnoea and TOI parameters for individual subjects.

TOI = tissue oxygenation index, CBV = cerebral blood volume, ΔTOI and ΔCBV are changes in TOI and CBV during apnoea defined as TOI dip, duration is duration of TOI dip, coeff is regression coefficient from simple linear regression.

id	ΔTOI/ΔCBV			TOI minimum/ΔCBV			Duration/ΔCBV		
	coeff	r^2	p	coeff	r^2	p	coeff	r^2	p
1	26.5	0.60	0.000	-22.2	0.62	0.000	58.33	0.41	0.000
2	10.29	0.13	0.05	68.97	0.06	0.22	174.1	0.09	0.11
3	16.5	0.26	0.001	-20	0.21	0.002	51.01	0.18	0.005
4	6.07	0.46	0.000	-3.22	0.06	0.13	53.34	0.47	0.000
5	-10.7	0.13	0.02	3.44	0.02	0.39	28.42	0.05	0.18
6	-1.91	0.01	0.49	0.44	0.00	0.87	-23	0.07	0.11
7	2.37	0.02	0.34	-5.11	0.04	0.24	6.29	0.01	0.64
8	5.73	0.08	0.07	-10.6	0.19	0.006	114.0	0.16	0.01

Changes in CBV correlate significantly with ΔTOI in 5 out of 8 subjects, with minimum TOI in 2 out of 8 subjects and with dip duration in half the subjects.

Significant correlations were also seen between CBV change and TOI change, minimum TOI and duration, in the whole group (Table 26).

Table 26. Regression coefficients for effect of CBV difference on TOI minimum, difference and duration of drop for 303 apnoeas corrected for interpatient differences.

TOI = tissue oxygenation index, CBV = cerebral blood volume, cytox = cytochrome oxidase, ΔTOI, Δcytox, and ΔCBV are changes in TOI, cytox and CBV during apnoea defined as TOI dip, TOImin is minimum TOI during apnoea, duration is duration of TOI dip. Coeff = regression coefficient. Regression was performed using the xtgee command of stata6 (146).

Effect	Coeff	95% CI	p
ΔCBV on Δcytox	0.373	0.108, 0.638	0.006
ΔCBV on TOI min	-8.58	-16.13, -1.04	0.026
ΔCBV on ΔTOI	9.84	2.95, 16.73	0.005
ΔCBV on duration	49.07	39.03, 59.11	<0.001

8.5.6 Temporal relationship

We wanted to assess how CBV change was temporally associated with TOI change. An increase in CBV would not necessarily increase oxygenation as it would depend on the saturation of the incoming blood. There are rapid swings in saturation during apnoea so it would be possible for incoming blood to increase or decrease overall oxygenation depending when during the apnea an increase in cerebral blood flow occurred. Figure 37 shows an example of one temporal relationship between CBV change and TOI change where the two traces are approximately 180 degrees out of phase. Figure 39, from a different subject, illustrates the second observed relationship, where CBV change is approximately in phase with TOI change.

Figures 40 and 41 show the result of cumulative averaging over consecutive apnoeas of the data shown in Figures 37 and 39. This illustrates the two different time relationships; in Figure 40 THb maximum occurs close to HHb maximum and TOI minimum; and in Figure 41 THb maximum coincides with OHb maximum as well as TOI maximum. Cytochrome oxidase changes in both cases are approximately in phase with TOI. The average TOI change over these 13 apnoeas is 12.8 in Fig 37 and 3.7 in Fig 39.

Figure 39. Raw NIRO data from subject 8

TOI = tissue oxygenation index, Cytox = cytochrome oxidase, OHb = oxygenated haemoglobin, HHb = deoxygenated haemoglobin, THb = total haemoglobin (OHb + HHb), all chromophores measured in μM from arbitrary baseline, TOI measured in %saturation.

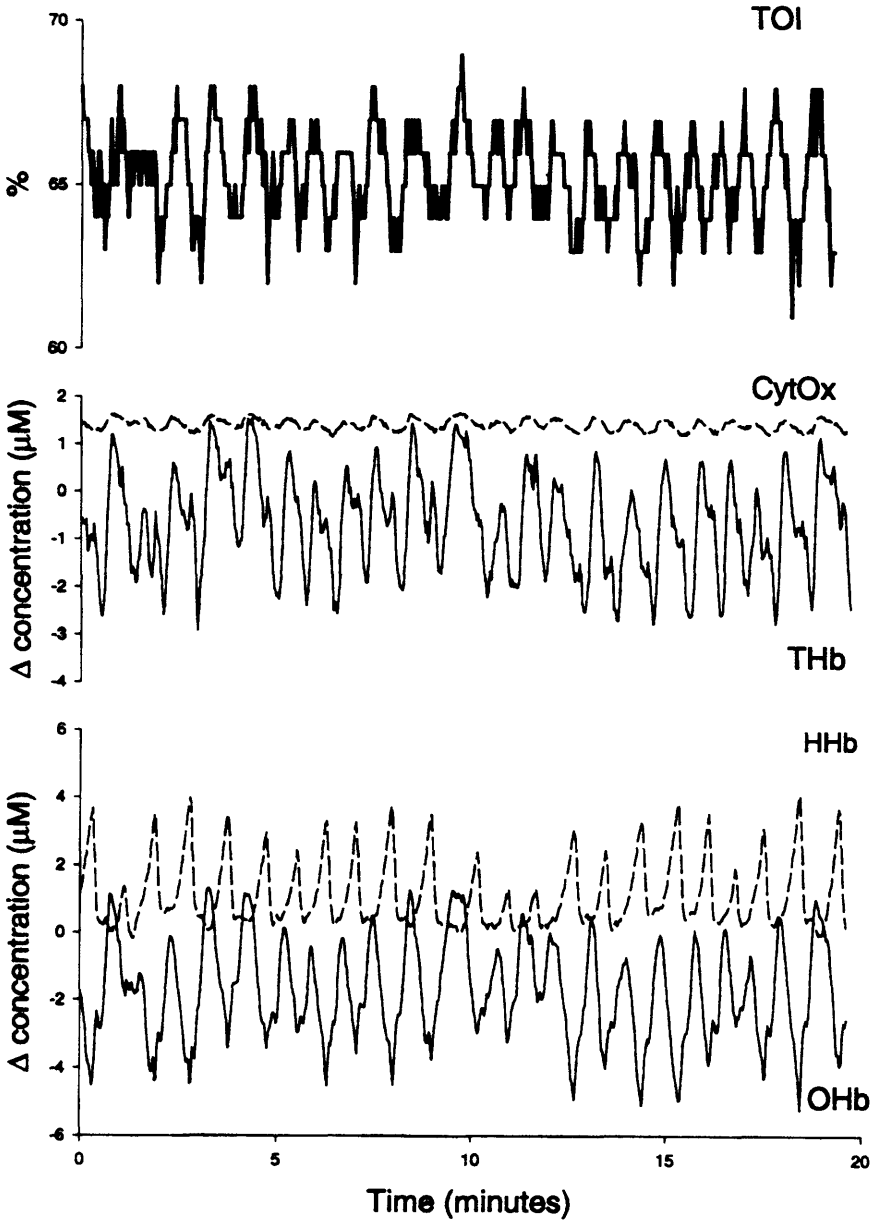


Figure 40. Cumulative average over consecutive apnoeas in subject 1 (See figure 34 for raw data)
TOI = tissue oxygenation index, Cytox = cytochrome oxidase, OHb = oxygenated haemoglobin, HHb = deoxygenated haemoglobin, THb = total haemoglobin (OHb + HHb), all chromophores measured in μM from arbitrary baseline, TOI measured in %saturation. Cytox enlarged by a factor of 5.

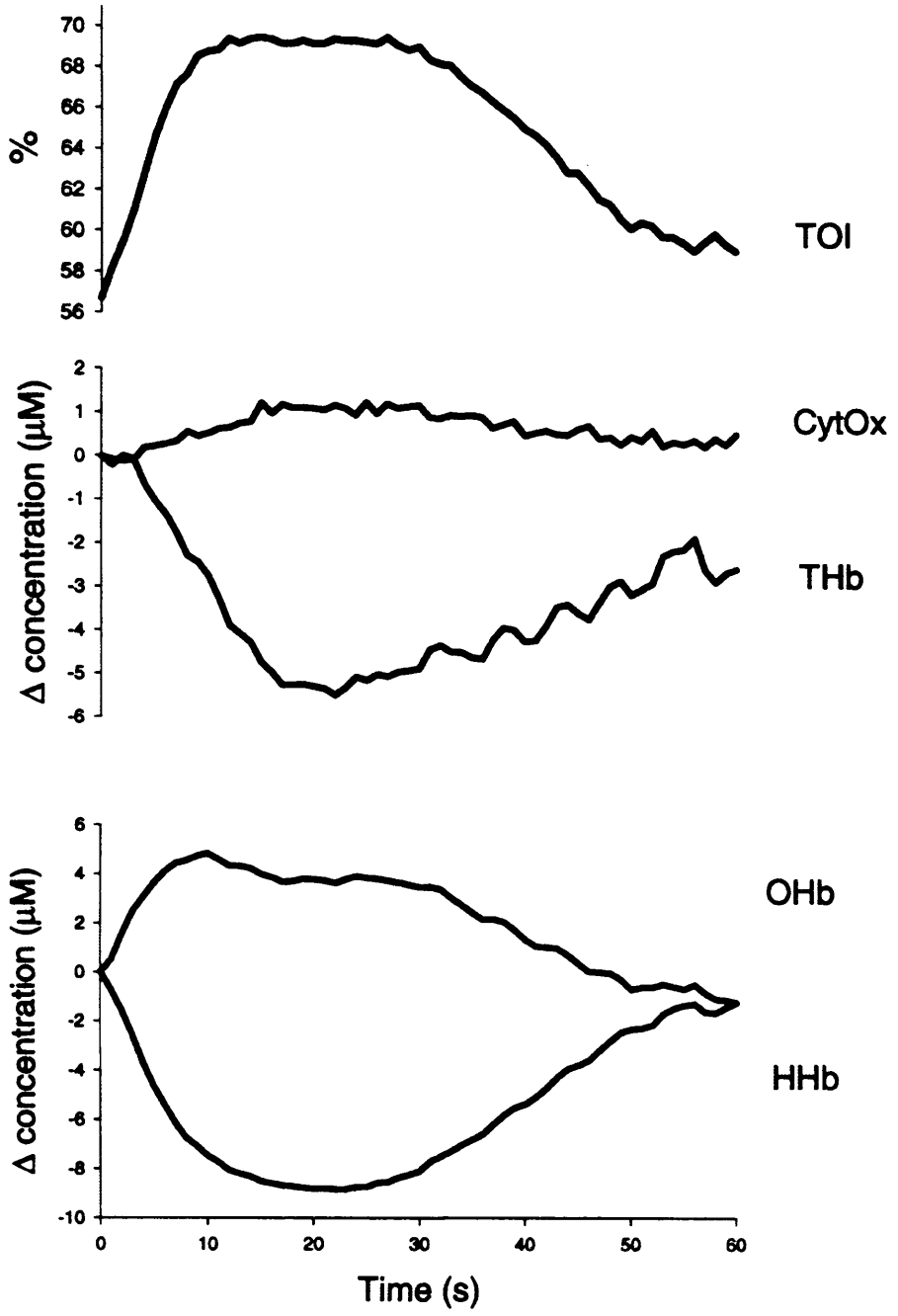
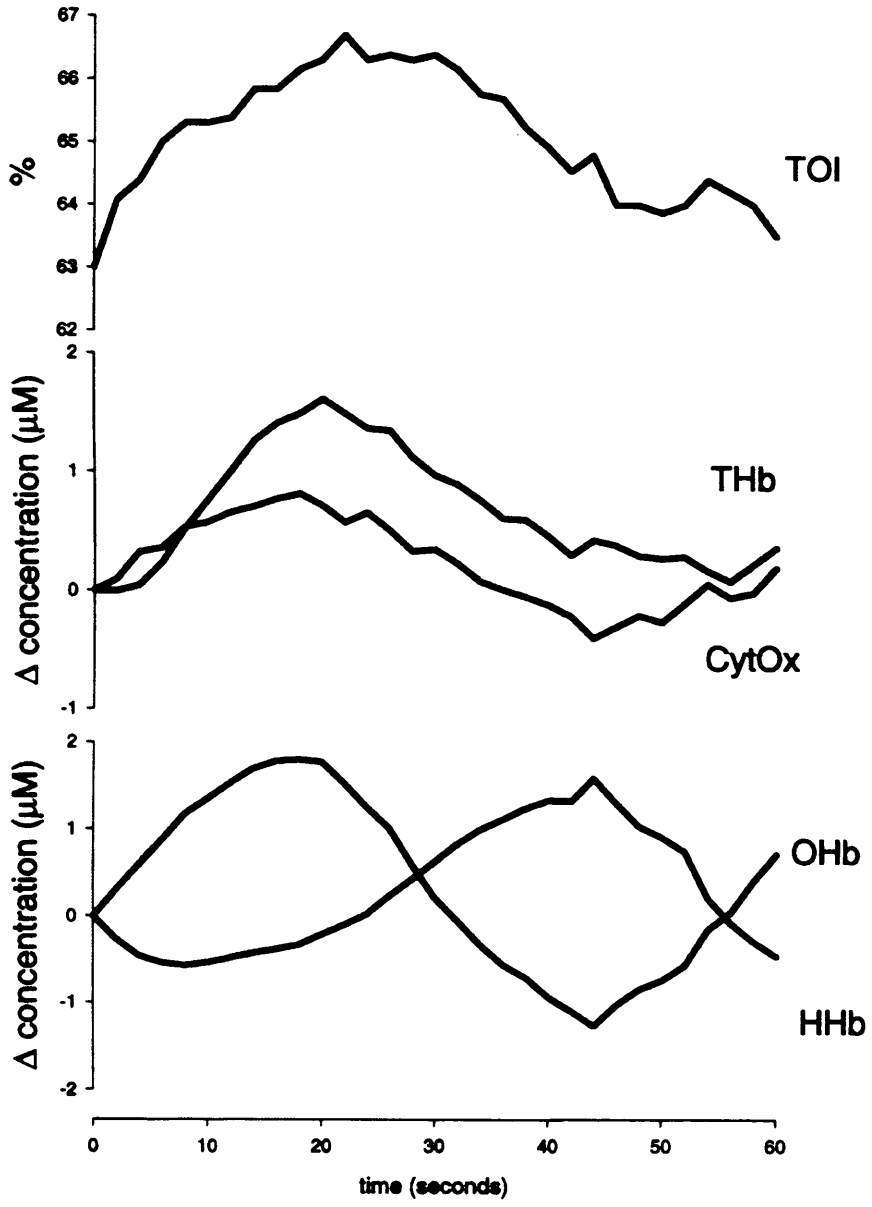


Figure 41. Cumulative average over consecutive apnoeas in subject 8 (See figure 36 for raw data).

TOI = tissue oxygenation index, Cytox = cytochrome oxidase, OHb = oxygenated haemoglobin, HHb = deoxygenated haemoglobin, THb = total haemoglobin (OHb + HHb), all chromophores measured in μM from arbitrary baseline, TOI measured in %saturation. Cytox enlarged by a factor of 5.



8.5.7 Redox changes in haemoglobin oxidation during CBV increase (OHbratio)

A measure of the distribution of the two patterns in the 303 apnoeas is given by the OHb ratio. OHb ratio is the ratio of the change in OHb occurring during the THb rise to the change in THB (or how much of the THb rise is oxygenated). In 86 apnoeas the OHbratio was less than 0, ie the OHb fell during the total haemoglobin rise, similar to Figure 40. In 67 apnoeas the OHbratio was >1 ie the HHb fell during the total haemoglobin rise, similar to Figure 41. In the remainder both OHb and HHb rose during the THb rise. The mean OHb ratio ranged from –0.15 (subject 1 illustrated in Figs 37 and 40) to 0.96 (subject 8, illustrated in Figs 39 and 41). The other subjects had a mixture of the two patterns, with mean OHbratios of 0.24 – 0.76 (Table 27).

Table 27. Average OHbratio in 8 subjects

OHb = oxygenated haemoglobin, THb = total haemoglobin, OHbratio is the ratio of OHb to THb in the THb change during apnoea. ΔTOI = change in tissue oxygenation index during apnoea

Id	Mean OHbratio	Mean ΔTOI
1	-0.15	12.22
5	0.24	5.43
3	0.43	6.93
2	0.47	7.76
7	0.54	4.33
4	0.73	5.48
6	0.76	5.3
8	0.96	4.05

There is a non-significant tendency for a higher mean OHbratio to be associated with a lower mean TOI drop in these 8 patients. When the apnoeas were divided into two groups above and below mean OHbratio, the effect of CBV change on TOI change was significantly greater in the group with low OHbratio (Table 28).

Table 28. Relationship between change in CBV and TOI change with apnoeas split into 2 groups by OHbratio.

CBV = cerebral blood volume, TOI = tissue oxygenation index, OHb = oxygenated haemoglobin, THb = total haemoglobin, OHbratio is the ratio of OHb to THb in the THb change during apnoea. ΔTOI and ΔCBV = changes in TOI and CBV during apnoea defined as TOI dip. Coeff = regression coefficient from simple regression.

Effect	Coeff	95% CI	p
ΔCBV diff on ΔTOI diff (OHbratio > mean)	5.83	3.51, 8.16	<0.001
ΔCBV diff on ΔTOI diff (OHbratio < mean)	18.44	11.59, 25.29	<0.001

If the incoming blood is well oxygenated it may partially compensate for the drop in cerebral oxygenation due to fall in SaO_2. If however the incoming blood is poorly oxygenated (because the CBF increase occurs at the end of the apnoea when in some subjects SaO_2 is very low) then it may exacerbate the cerebral hypoxia due to reduced SaO_2. This early pilot work suggests that the CBF increase could both compensate and exacerbate hypoxia during apnoeas and that some patients had predominantly compensation, some exacerbation and some a mixture. However this work was based on tHb as a proxy for CBF and there are theoretical problems with this, principally extracranial contamination of the signal. We therefore went on to look at the effect of CBF change on TOI in more detail in a further validation study (Chapter 9).

8.6 SUMMARY

8.6.1 Changes in intracellular redox state measured using cytochrome oxidase redox state are seen during obstructive sleep apnoea.

In this chapter we demonstrated changes in cytochrome oxidase oxidation state that occur during apnoea and correlate with changes in cerebral oxygenation measured as TOI. These changes were small (0.13 – 0.48 micromolar) but are interesting as a demonstration of changes in intracellular metabolism during OSA.

8.6.2 There is not a fixed temporal relationship between changes in total haemoglobin and measures of oxygenated haemoglobin during obstructive sleep apnoea

Using the haemoglobin signals from NIRS it is possible to derive a total haemoglobin measurement (OHb + HHb). Changes in THb in the field studied can be assumed to be due to changes in cerebral blood volume. If cerebral blood flow is not being measured, these CBV changes can be used as a proxy for CBF changes. We described changes in CBV during apnoea of 0.41-0.09 ml/100g and showed an overall correlation between CBV changes and TOI changes. We explain this by postulating that changes in CBF will affect cerebral oxygenation. We also showed that the proportion of Ohb in the THb change varies in different apnoeas, and quantified this proportion as Ohbratio. This variation occurs because there are cyclical changes in both SaO_2 and CBF during repetitive apnoeas, and the extent of desaturation varies between different subjects. We showed that a negative Ohbratio was associated with a bigger TOI dip, and this is consistent with the suggestion that in some apnoeas haemodynamic changes exacerbate rather than compensate for hypoxia. This reinforces the idea that these CBF changes are largely passive rather than autoregulatory and that they do not necessarily even partially protect the brain from hypoxia.

We also used the technique of cumulative averaging to illustrate two different patterns of TOI change and THb change during apnoea, showing by another method that in some apnoeas the THb change occurs at maximum TOI (and may compensate for hypoxia) and in others it occurs at minimum TOI (and may exacerbate hypoxia). The initial hypothesis was therefore shown to be false. This finding adds to the evidence supporting the fact that measuring cerebral oxygenation during OSA provides more information than pulse oximetry alone.

This is a large amount of very detailed analysis on the raw NIRO data. In order to proceed further in investigating the importance of cerebral blood flow changes in cerebral oxygenation in OSA it was necessary to measure cerebral blood flow more directly. The relationship between pulse oximetry, NIRO and Doppler cerebral blood flow velocity is described in the next chapter.

9. PROTOCOL AND RESULTS OF SECOND VALIDATION STUDY USING NIRS IN OSA WITH SIMULTANEOUS MEASUREMENT OF DOPPLER CEREBRAL BLOOD FLOW VELOCITY.

9.1 OVERALL HYPOTHESIS

9.1.1 Measurement of cerebral oxygenation using near-infra red spectroscopy gives additional valid information compared to measurement of arterial oxygen saturation alone

9.2 INTRODUCTION

This chapter contains a description of underlying hypotheses, protocols, data analysis and results of the second validation study which aimed to validate the NIRO 300 as a measure of intracerebral oxygenation in OSA using Doppler cerebral blood flow velocity measurements (CBFV). 8 subjects underwent NIR cerebral oxygen monitoring with simultaneous measurement of pulse oximetry, CBFV using Doppler, laser Doppler flow, arterial blood pressure and airflow during daytime naps.

9.3 HYPOTHESES UNDERLYING ANALYSIS.

9.3.1 Background.

The second validation study was carried out with two main aims. Our neurosurgical collaborators were interested in validation of the NIRO300 in a physiological system other than carotid endarterectomy. In their previous validation studies in neurosurgery both SaO_2 and ABP were constant and controlled (111). Validation was based on showing the TOI to be affected by changes in intracranial circulation (CBFV) and not by changes in extracranial circulation (measured as cutaneous circulation using laser Doppler flow). CBFV is affected by ABP changes, although it also depends on autoregulatory changes, whereas cutaneous flow is passively dependent on ABP. We would therefore predict that TOI would be more closely related to CBFV than to ABP in sleep apnoea, and that LDF measurements would be related to ABP. Validation of the NIRO300 will depend on these relationships and also on the temporal relationships between the changes of these parameters. As researchers into sleep apnoea physiology, our aim was to see if the CBFV changes which are known to occur in sleep apnoea are associated with cerebral oxygenation changes, and if so whether they compensated for or exacerbated the effects of arterial hypoxaemia on cerebral oxygenation. The analysis required to achieve both these aims was very similar; they are, in a way, two ways of interpreting the same results.

9.3.2 TOI changes are affected by changes both in cerebral blood flow and in arterial saturation.

This was investigated by examining the relationship between TOI, CBFV and SaO_2. Theoretically cerebral oxygenation depends on both arterial saturation and cerebral blood flow. This analysis has the dual aim of demonstrating this relationship for the first time during the dynamic changes that occur in OSA and validating the NIRO300 TOI as a measure of cerebral oxygenation.

9.3.3 TOI changes are not affected by extracranial changes

This was investigated by examining the interrelationships of ABP, LDF, CBFV and TOI, to see if TOI is obviously affected by extracranial changes. This was done both by looking at absolute changes in parameters during apnoea, and also looking at the temporal relationships using cumulative averaging as described below. We were also able to look at the effects of $etCO_2$ on TOI and CBFV.

9.3.4 THB (relative cerebral blood volume) can be used as a proxy for changes in CBFV, (as used in chapter 8).

We were able to check using the CBFV readings whether the assumption that THb could be used as a proxy for cerebral blood flow was valid. We were also interested in checking the validity at OHbratio,a measure of the redox status of the change in total haemoglobin which occurs during apnoea, which was postulated to influence the effect of the increased cerebral blood flow on cerebral oxygenation during apnoea (see chapter 8).

9.3.5 Changes in cytochrome oxidase redox state during obstructive sleep apnoea are related to cerebral oxygenation measured independently of NIRS

We related changes in cytochrome oxidase redox state to changes in CBFV and in SaO_2 during apnoea. We had shown in chapter 8 relationships between cerebral oxygenation as TOI and changes in cytox redox state during OSA. As both were measured using NIRS, we wished in this second validation study to relate cytox to components of cerebral oxygenation (SaO_2 and CBFV) measured independently of NIRS.

9.4 COLLABORATION

This study was carried out in collaboration with Mr P Kirkpatrick and the University Department of Neurosurgery, Addenbrooke's Hospital. The study was performed by myself and Pippa Al-Rawi, Research Associate from the Department of Neurosurgery, Addenbrooke's, under the supervision of Mr Kirkpatrick (Cambridge) and Professor S Spiro and Dr H Makker (UCLH). Work was carried out in the Sleep Unit at the Middlesex Hospital over a period of 2 weeks in October 2000.

9.5 SUBJECTS

8 men with significant OSA (mean 4% oxygen desaturation dip rate 71 +/- 19) and no known cerebrovascular disease problems were recruited from our sleep clinic population. One subject with mild OSA also participated at short notice. Suitable subjects with severe OSA were informed of the opportunity to participate in the study by letter and telephone. An attempt was made to contact the people who had participated in the previous study of whom 5 agreed to participate. Seven stopped using their therapeutic CPAP 2 nights prior to the study, two were not on current treatment. Venous blood was drawn for full blood count at the time of the study. Characteristics and comorbidities of the subjects are shown in table 29 and 30.

Ethical approval was granted by the relevant ethics committee and all subjects gave written consent.

Table 29. Subjects who took part in second validation study.

Subjects who also took part in the first validation study are marked with an asterisk. All were men.

ID	Age /yrs	BMI kg/m^2	Dip rate /hr	ESS	Hb/ g/dl	CPAP
1.CM*	57	33.8	66	19	13.1	Y
2.DH	48	47.7	66	15	14.7	Y
3.DS*	57	31.5	40	15	15.7	Y
4.GD*	44	36.8	74	14	15.7	Y
5.JP	56	43.9	45	8	15.3	N
6.PH*	32	36.6	87	19	15.4	Y
7.SM*	40	39.1	95	21	15.3	Y
8.SZ	56		16		13.6	N

Table 30. Comorbidity of subjects

ID	*Cerebrovascular disease*	*Ischaemic heart disease*	*hypertension*
CM 1	n	y	n
DH 2	n	n	n
DS 3	n	n	n
GD 4	n	n	n
JP 5	n	n	y
PH 6	n	n	n
SM 7	n	n	n
SZ 8	n	y	y

9.6 PROTOCOL FOR RECORDING AND ANALYSIS

9.6.1 Recording protocol

The following monitoring devices were used as described in chapters 3 and 4:

(a) NIRO 300, recording oxygenated and deoxygenated haemoglobin, cytochrome oxidase and TOI signals every 2 seconds into a data acquisition system.

(b) Pulseox 7 (Minolta, now Anandic Medical Systems, Diessenhofen, Switzerland) pulse oximeter using both finger and ear probes.

(c) Middle cerebral artery flow velocity using a transcranial doppler probe (PCDop 842, Scimed, Bristol, UK) over the middle cerebral artery, held in place by a custom-made head-band.

(d) Scalp blood flow using laser doppler flowmetry (MBF3D monitor and modified P3 probe, Moor Instrument Ltd, Axminster, Devon, UK), with the probe placed in the immediate vicinity of the NIR optodes.

(e) Blood pressure was monitored continuously using a non-invasive Finapres BP monitor (Ohmeda 2300, Boulder Colorado USA).

(f) End tidal carbon dioxide monitoring, using Capnosleep, (Weinmann, Germany).

(g) Sleep staging, using EEG, EOG, EMG (S Series Sleep System, Compumedics®, Melbourne, Victoria, Australia)

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The monitoring equipment was connected and subjects were asked to lie down in a darkened side room and allowed to sleep for up to 2 hours. The Doppler probe was sited by an experienced operator and continuously observed throughout the recording period. All the parameters were simultaneously recorded onto a data acquisition system, except for the EEG, EOG and EMG which were recorded on to the polysomnography computer.

9.6.2 Methods for analysis

Sleep was staged using standard criteria. Data from one subject was unusable for technical reasons. One subject (Subject 8) did not demonstrate any obstructive events during 52 minutes of sleep and his data were analysed separately. Apnoeas were defined as cessation of airflow for 10s from the capnogram trace. For the remaining 7 subjects, baseline values of SaO_2, cerebral blood flow velocity (CBFV), mean arterial blood pressure (ABP), and tissue oxygenation index (TOI) were obtained by averaging values over 10 seconds from the initial part of the recording while the subjects were awake. Maximum and minimum values of SaO_2, CBFV, ABP, TOI, cytochrome oxidase and total haemoglobin were recorded for each apnoea that occurred during sleep in these 7 subjects (287 apnoeas in total, 6-59 per subject). $EtCO_2$ was recorded before and after each apnoea. Absolute changes in each parameter were then calculated for each apnoea and averaged for each subject. The relationship between changes in TOI and changes in CBFV, ABP, SaO_2 and total haemoglobin, were examined, initially using a single independent variable and then multiple variables, using two level regression adjusting for subject (111). Relationships between $etCO_2$ and both CBFV and TOI were also examined. The relationships between changes in CBFV, ABP and total haemoglobin were examined, as were those between changes in CBFV, SaO_2 and cytochrome oxidase.

OHbratio was calculated as described in chapter 5 as the change in OHb which occurred during the THb rise, expressed as a fraction of the THb rise and signed to distinguish between a rise and a fall in OHb.

In 5 subjects who all showed runs of consecutive apnoeas, a cumulative average of readings of CBFV, ABP, TOI, SaO_2 and laser Doppler flow from the raw data was

calculated over a run of consecutive apnoeas (9-18 apnoeas). This cumulative average was then plotted to illustrate the time relationship between the changes.
Twenty-six episodes of repetitive change in CBFV were analysed for the subject who did not demonstrate oxygen saturation changes (subject 8). For each of these episodes, maximum and minimum SaO_2, TOI, CBFV and ABP were recorded, and changes in these parameters were compared using regression analysis as above.

9.6.3 Statistics

Baseline variability was assessed using coefficient of variability.
Changes in parameters and mean minimum and mean preapnoea values of TOI were expressed as mean plus SD.
Changes in parameters were analysed separately in each subject using scatterplots to check the relationships were approximately linear followed by simple regression analysis.
Apnoeas were then combined as described previously in a two level regression adjusting for subject.
Cumulative averaging was used for illustrative purposes only and significance testing was not performed.
Acceptable level of significance was taken as $p<0.05$.

9.7 RESULTS

9.7.1 Descriptive sleep data

Descriptive sleep data was available for 7 of the 8 subjects whose data were analysed (Table 31). They slept for an average of 57 minutes (range 12 to 83). One subject had a sleep latency of 45 minutes, in the remainder sleep latency was < 5 minutes. No subjects demonstrated REM sleep during these daytime naps. Mean AHI during the recording was 66 (range 34 – 118). Respiratory event data is given in Table 32.

Table 31. Descriptive sleep data for subjects.

The staging polysomnography was technically inadequate for subject 7. REM = rapid eye movement, n/a = not available.

ID	*Sleep latency/min*	*Total sleep/min*	*Stage1 min*	*Stage2 min*	*Stage3 min*	*Stage4 min*	*REM min*
CM 1	0.3	82.7	41.7	41	0	0	0
DH 2	2.3	53.7	7.0	27.0	19.7	0	0
DS 3	0	12.0	11.7	0.3	0	0	0
GD 4	0.3	74.7	19.0	54.7	1.0	0	0
JP 5	1.3	49.3	6.3	30.3	12.3	0.3	0
PH 6	0.3	70.0	1.3	33.3	35.3	0	0
7	n/a						
SZ 8	0	52.3	8.0	18.3	26	0	0

Table 32. Respiratory event data for 7 of 8 subjects.

Mean min sat = mean minimum SaO_2 during apnoea, av desat = average SaO_2 desaturation during apnoea.

ID	*Apnoea index /hour*	*Hypopnoea index /hour*	*AHI /hour*	*Mean min sat*	*Av desat*	*Mean apnoea duration/s*
1	49.4	8.7	58.1	88.1	7.2	21
2	33.3	43.3	76.7	84	9.5	14.5
3	20.0	15.0	35.0	89	3	12.9
4	71.5	6.4	77.9	84	9.5	17.6
5	29.2	4.9	34.1	86.3	5.7	15.9
6	95.1	23.1	118.3	85	4.5	16.8
7						
8	0	0	0	90.6	0	0

9.7.2 Baseline measurements, variability and changes during apnoea (TOI, SaO_2, CBFV, ABP)

Baseline mean arterial blood pressure ranged from 75.7-106.6 mmHg (Table 33) and the changes during apnoea ranged from 17.5+/- 6.1 to 30.6+/-7.5 mmHg (Table 34). The range of baseline CBFV was 30.2 - 78.6m/s, where changes during apnoea (ΔCBFV) ranged from 12.5 +/- 3.4 to 30.2 +/- 6.0m/s. The maximum drop in CBFV as a fraction of baseline ranged from 32 to 50% for the 7 subjects, with a mean drop of 8 to 40%. Baseline SaO_2 values were all above 94% (range 94.8-99.6) where baseline TOI values ranged from 60.8-84.0. The range of mean SaO_2 drops (Δ SaO_2) during apnoea was 1.7 +/- 0.4 to 12.1 +/- 3.8; that of mean TOI drops (ΔTOI) was 2.3+/-0.5 to 5.0+/- 2.0 (Table 34).

There was no correlation between values of SaO_2 and TOI preceding apnoea, however minimum TOI correlated with minimum SaO_2 during an apnoea after adjusting for interpatient differences ($p<0.001$, regression coefficient 0.215, 95%CI 0.132-0.298). Median coefficient of variation of TOI over 100 observations in 6 subjects was 1.22% (range 0.58 – 1.35). The mean coefficient of variation of CBFV in 6 subjects over 100 observations during unobstructed breathing was 6.7% (range 4.22 – 10.5%).

Table 33. Baseline awake values for measured parameters

ABP = arterial blood pressure, CBFV = cerebral blood flow velocity, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index.

ID	ABP mmHg	CBFV m/s	SaO_2 %	TOI %
1	75.7	53.2	97.3	67.8
2	87.4	69.2	94.8	72.4
3	82.3	38.1	99.6	82.7
4	87.4	49.7	96.7	73.5
5	102	30.2	95.6	84
6	106.6	78.6	96.5	71.4
7	87	59.8	96.7	60.8

Table 34. Mean minimum SaO_2 and TOI, mean TOI preceding apnoea, and mean changes in ABP, CBFV, SaO_2 and TOI during apnoea.

ABP = arterial blood pressure, CBFV = cerebral blood flow velocity, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index. Mean min SaO_2 and TOI are mean of minimum value for each apnoea, mean baseline TOI is maximum value preceding each apnoea. ΔABP, ΔCBFV, Δ SaO_2 and ΔTOI are changes during apnoea, duration is apnoea duration from capnogram.

ID	No. of apnoeas	Mean min SaO_2 %	Mean baseline TOI %	Mean min TOI %
1	54	88.5 +/- 4.7	67.2 +/- 2.5	62.9 +/- 2.6
2	46	87.9 +/- 2.8	68.6 +/- 1.3	64.2 +/- 1.7
3	6	96 +/- 0.4	83.3 +/- 1.7	81 +/- 2.0
4	57	84.8+/- 3.5	76.8 +/- 3.0	71.9 +/- 2.8
5	16	89.1+/- 3.2	81.5 +/- 2.9	77.4 +/- 3.1
6	59	92.2+/- 3.1	71.9 +/- 1.2	69.6 +/- 1.4
7	49	82.7 +/- 3.9	59.6 +/- 1.0	56.4 +/- 1.5

ID	No. of apnoeas	Mean ΔABPmmHg	Mean ΔCBFV m/s	Mean ΔSaO2 %	Mean ΔTOI %	Mean duration s
1	54	25.9 +/- 4.9	18.0 +/- 4.3	9.1 +/- 4.8	4.3 +/- 1.6	25 +/- 8.8
2	46	20.1 +/- 5	23.0 +/- 3.9	10.6 +/- 1.9	4.4 +/- 1.2	16 +/- 4.2
3	6	17.5 +/- 6.1	15.6 +/- 4.8	1.7 +/- 0.4	2.4 +/- 0.8	11 +/- 3.2
4	57	24.1 +/- 8.7	26.0 +/- 7.3	10.3 +/- 3.5	5.0 +/- 2.0	16.2 +/- 5.6
5	16	24.6 +/- 4.2	12.5 +/- 3.4	8.4 +/- 3.3	4.1 +/- 1.4	16.8 +/- 5.4
6	59	27.6 +/- 5.5	30.2 +/- 6.0	7.1 +/- 3.1	2.3 +/- 0.5	16.6 +/- 4.6
7	49	30.6 +/- 7.5	25.5 +/- 8.1	12.1 +/- 3.8	3.2 +/- 1.0	16.8+/- 5.2

9.7.3 Relationships between changes in TOI and changes in other measured parameters

When data was analysed separately for each subject, the relationship between ΔTOI and ΔCBFV and the relationship between ΔTOI and Δ SaO_2 were significantly positive in 5 of the 7 subjects. The relationship between ΔTOI and ΔABP was significant in 2 subjects. Combining all 287 apnoeas using simple regression adjusting for interpatient differences the magnitude of ΔTOI during an apnoea correlated with the magnitude of Δ SaO_2, ΔCBFV, ΔABP and duration of apnoea ($p<0.001$ in all cases; Table 35).

Table 35. Relationships between changes in TOI and changes in other measured parameters

ABP = arterial blood pressure, CBFV = cerebral blood flow velocity, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index. SaO_2min is minimum value of SaO_2 for each apnoea. ΔABP, ΔCBFV, Δ SaO_2 and ΔTOI are changes during apnoea, duration is apnoea duration from capnogram. OHb = oxygenated haemoglobin, THb = total haemoglobin, OHbratio is the ratio of OHb to THb in the THb change during apnoea. Pairs of parameters during apnoeas in different subjects were combined in a two level simple regression using the xtgee command of stata6(146). Coeff = regression coefficient.

Dependent variable	Independent variable	Coeff	95% CI	P
ΔTOI	ΔSaO_2	0.176	0.112,0.241	<0.001
ΔTOI	ΔCBFV	0.063	0.043, 0.083	<0.001
ΔTOI	ΔABP	0.058	0.034,0.081	<0.001
ΔTOI	duration	0.204	0.116,0.293	<0.001
ΔTOI	OHbratio	-0.271	-0.734,0.191	0.25
ΔTOI	SaO_2min	-0.189	-0.245,-0.133	<0.001

As mentioned before, trying to separate intracranial and extracranial contributions to TOI changes is complicated by the changes in ABP and SaO_2 during apnoea which are associated with/cause change in CBFV (Table 36).

Table 36. Relationships between changes in CBFV and changes in other measured parameters.

ABP = arterial blood pressure, CBFV = cerebral blood flow velocity. SaO_2min is minimum value of SaO_2 for each apnoea. ΔABP, ΔCBFV are changes during apnoea, duration is apnoea duration from capnogram. Pairs of parameters during apnoeas in different subjects were combined in a two level simple regression using the xtgee command of stata6(146). Coeff = regression coefficient.

Dependent variable	Independent variable	Coeff	95% CI	P
ΔCBFV	ΔABP	0.379	0.308,0.450	<0.001
ΔCBFV	duration	0.618	0.078,1.16	0.03
ΔCBFV	SaO_2min	-0.515	-0.857,-0.174	0.003

Using multiple regression including duration, ΔCBFV and Δ SaO_2 as independent variables, these 3 factors retained a significant effect on ΔTOI difference (Table 32).

Table 37. Two level regression models showing effect of ΔCBFV, duration and ΔSaO_2 on ΔTOI

CBFV = cerebral blood flow velocity, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index. Parameters during apnoeas in different subjects were combined in a two level multiple regression using the xtgee command of stata6(146). Coeff = regression coefficient.

Independent variable	Coeff	95%CI	P
Duration	0.137	0.055,0.219	0.001
ΔCBFV	0.015	0.003,0.014	0.012
Δ SaO_2	0.129	0.053,0.206	0.001

9.7.4 Cytochrome oxidase and THb measurements

Cytochrome oxidase measurement started from an arbitrary baseline of 0 at the beginning of each recording. Concentration changes in cytochrome oxidase ranged from 0.18±0.08 to 0.08±0.03μM (Table 38). The median standard deviation of the cytox signal during 2

minutes (120 observations) of non-obstructed breathing in 6 subjects was 0.046 μM (range 0.021 to 0.076). Changes in THb ranged from 1.0 +/- 0.78 to 2.9 +/-1.5μM.

Table 38. Measured changes in cytox and THb during apnoea.

Cytox = cytochrome oxidase, ThB = total haemoglobin, TOI = tissue oxygenation index. Δcytox, ΔTHb and ΔTOI are changes occurring during apnoea defined by capnogram trace.

ID	No. of apnoeas	Mean Δcytox μM	Mean ΔTHb μM	Mean ΔTOI
1	54	0.08 +/- 0.03	1.0 +/- 0.78	4.3 +/- 1.6
2	46	0.14 +/- 0.06	1.1 +/- 0.3	4.4 +/- 1.2
3	6	0.11 +/- 0.06	1.5 +/- 0.4	2.4 +/- 0.8
4	57	0.17 +/- 0.08	2.2 +/- 1.0	5.0 +/- 2.0
5	16	0.17 +/- 0.1	2.8 +/- 1.6	4.1 +/- 1.4
6	59	0.14 +/- 0.08	2.9 +/- 1.5	2.3 +/- 0.5
7	49	0.19 +/- 0.08	2.2 +/- 0.9	3.2 +/- 1.0

Changes in THb were much better correlated with changes in ABP than with changes in CBFV. Cytox changes correlated with changes in TOI, CBFV and SaO_2 ($p<0.01$) and with ABP ($p<0.05$) (Table 39).

Table 39. Relationships between changes in cytox and THb and other measured changes.

ABP = arterial blood pressure, CBFV = cerebral blood flow velocity, SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, cytox = cytochrome oxidase, THb = total haemoglobin. ΔABP, ΔCBFV, Δ SaO_2, ΔTOI, Δcytox and ΔTHb are changes during apnoea, duration is apnoea duration from capnogram. Pairs of parameters during apnoeas in different subjects were combined in a two level simple regression using the xtgee command of stata6(146). Coeff = regression coefficient.

Dependent variable	Independent variable	Coeff	95% CI	p
ΔTHb	ΔCBFV	0.275	0.007,0.542	0.044
ΔTHb	ΔABP	0.352	0.150,0.555	0.001
ΔTOI	ΔTHb	0.028	-0.013,0.068	0.18
Δcytox	ΔTOI	0.432	0.160,0.704	0.002
Δcytox	ΔCBFV	0.083	0.035,0.130	0.001
Δcytox	ΔSaO_2	0.189	0.105,0.272	<0.001
Δcytox	duration	0.125	-0.114,0.363	0.3
Δcytox	ΔABP	0.076	0.007,0.146	0.03

9.7.5 OHbratio

Unlike in the previous validation study, OHbratio did not predict the steepness of the relationship between ΔTOI and either ΔTHb or ΔCBFV.

9.7.6 End tidal CO_2

The $etCO_2$ immediately preceding apnoea correlated with the maximum CBFV during apnoea (regression coefficient 0.156 (0.031-0.281) p=0.015), but there were no significant correlations with the $etCO_2$ following apnoea, or between TOI and $etCO_2$ variables. A possible correlation between $etCO_2$ at the start of apnoea and change in cytochrome redox state was found (regression coefficient -0.068, 95% CI -0.137 - 0.001, p=0.053),but no relationship between $etCO_2$ at the end of apnoea and cytochrome changes.

9.7.7 Cumulative average

The use of 2 point correlations to compare changes in different parameters is a simplified method for analysis, as changes in SaO_2 and CBFV occur at different times during the apnoea and may be separately reflected in the TOI trace. One subject shows a biphasic waveform for TOI particularly clearly (subject 2, Fig 42). A cumulative average of these apnoeas is shown in Fig 43. Fig 43 also shows ABP and LDF averaged traces, and illustrates graphically that the ABP and LDF traces lag behind the CBFV and TOI traces. In Fig 43 SaO_2 maximum occurs at timepoint 3, TOI and CBFV maxima at time point 11, and ABP and LDF maxima at time point 15. In 4 other subjects who showed consecutive apnoeas, the lag between the CBFV and ABP traces is less obvious, but in 3 subjects (subjects 1,Fig 44; 4, Fig 45; 7,Fig 46) the TOI trace can be seen to rise during the initial part of the CBFV rise and then fall as CBFV and ABP reach a maximum. In the 4th subject (subject 6, Figure 47) the CBFV peak is reached early during the SaO_2 desaturation and there is minimum alteration in the averaged TOI trace. Subjects 3 and 5 had only 6 and 16 apnoeas respectively and did not demonstrate any runs of consecutive events.

Figure 42. Raw data from subject 2

This illustrates the raw data output recorded every 2s. Abp = (mean) arterial blood pressure, fv = cerebral blood flow velocity, SaO_2 = arterial oxygen saturation, toi = tissue oxygenation index. Units on the y axis are mmHg for abp, m/s for fv, % for SaO_2 and % for TOI.

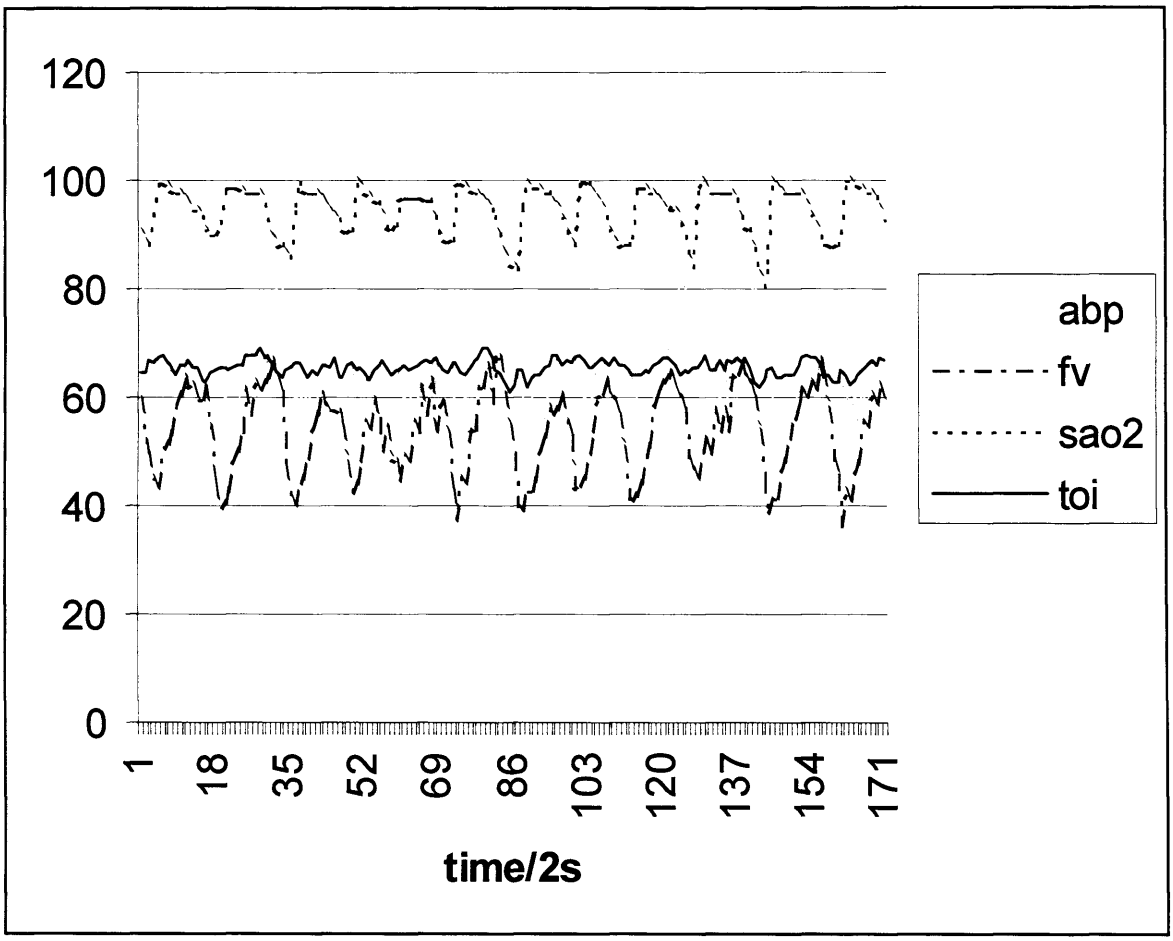


Figure 43. Cumulative average for subject 2 (16 apnoeas)

16 apnoeas averaged every 2s with minimum SaO_2 at time 0 to illustrate the temporal relationship of changes in different parameters. Sat = arterial oxygen saturation, toi = tissue oxygenation index, cbfv = cerebral blood flow velocity, abp = (mean) arterial blood pressure, ldf = laser doppler flow. Units on the y axis are % for $SaO_2$and % for TOI, m/s for cbfv, mmHg for abp, and arbitrary units for ldf.

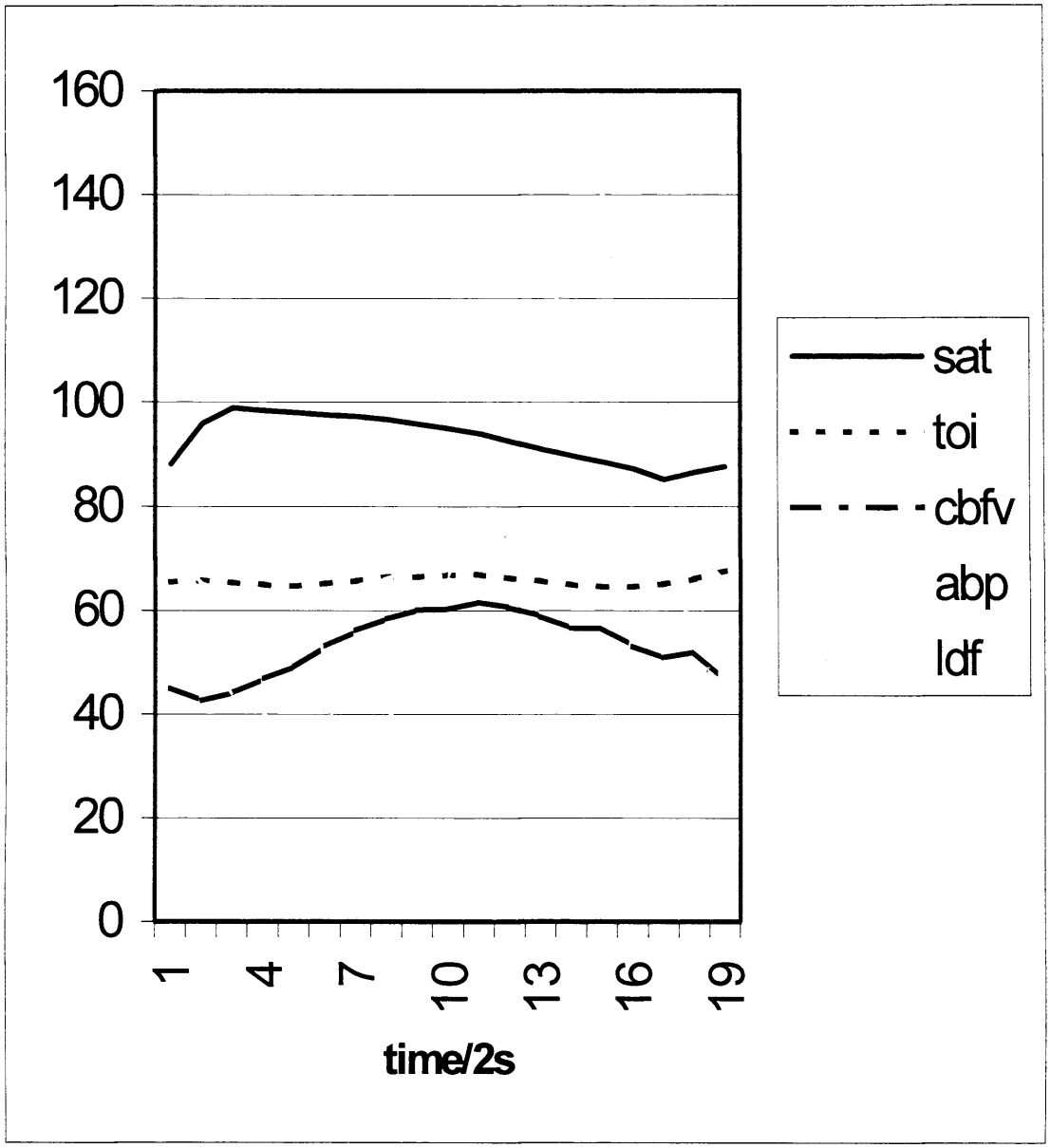


Figure 44. Cumulative average from subject 1 (10 apnoeas)

10 apnoeas averaged every 2s with minimum SaO_2 at time 0 to illustrate the temporal relationship of changes in different parameters. SaO_2 = arterial oxygen saturation, toi = tissue oxygenation index, cbf = cerebral blood flow velocity, abp = (mean) arterial blood pressure, ldf = laser doppler flow. Units on the y axis are % for SaO_2 and % for TOI, m/s for cbf, mmHg for abp, and arbitrary units for ldf.

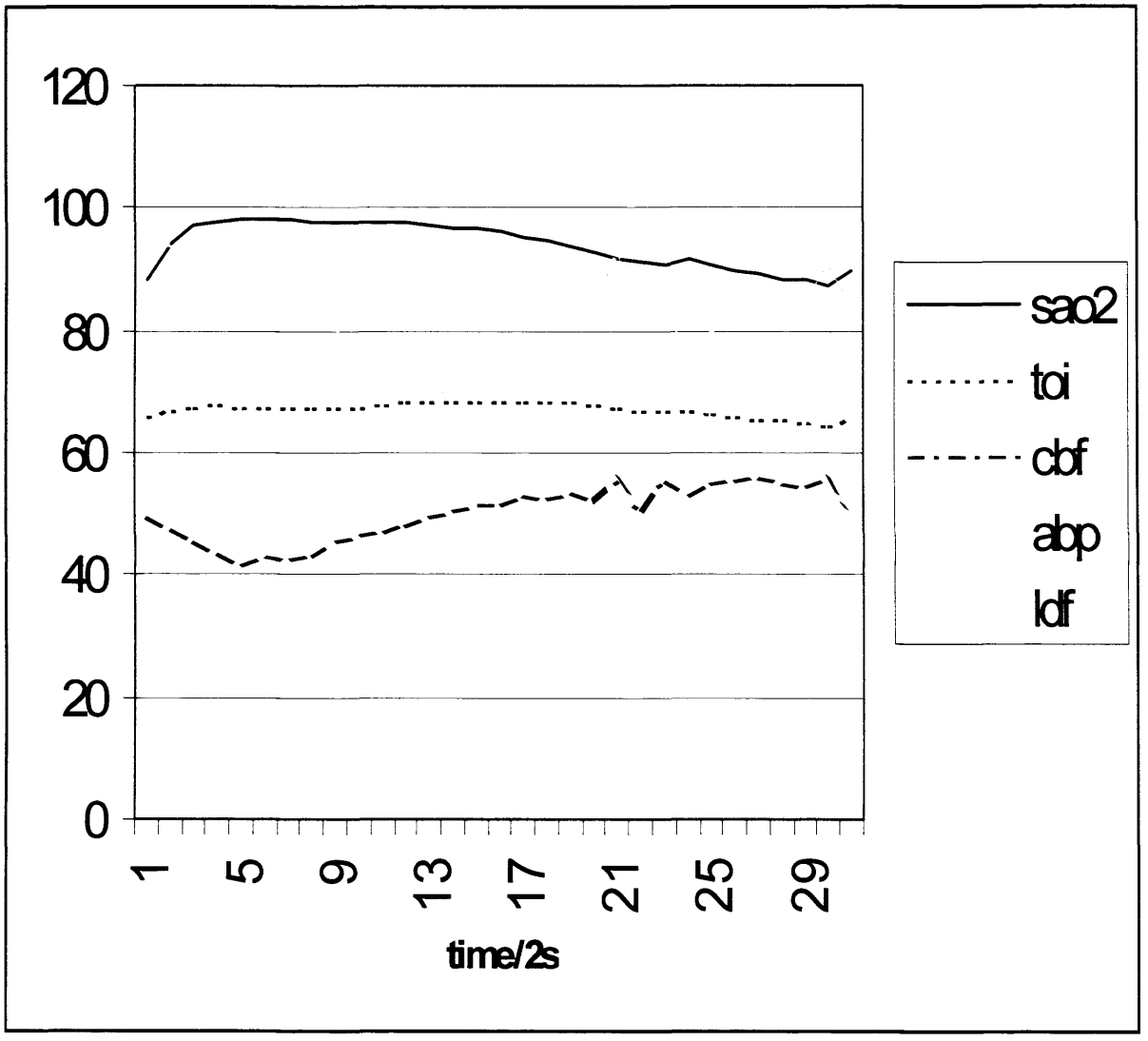


Figure 45. Cumulative average from subject 4 (9apnoeas)

9 apnoeas averaged every 2s with minimum SaO_2 at time 0 to illustrate the temporal relationship of changes in different parameters. SaO_2 = arterial oxygen saturation, toi = tissue oxygenation index, fv = cerebral blood flow velocity, abp = (mean) arterial blood pressure, ldf = laser doppler flow. Units on the y axis are % for SaO_2 and % for TOI, m/s for fv, mmHg for abp, and arbitrary units for ldf.

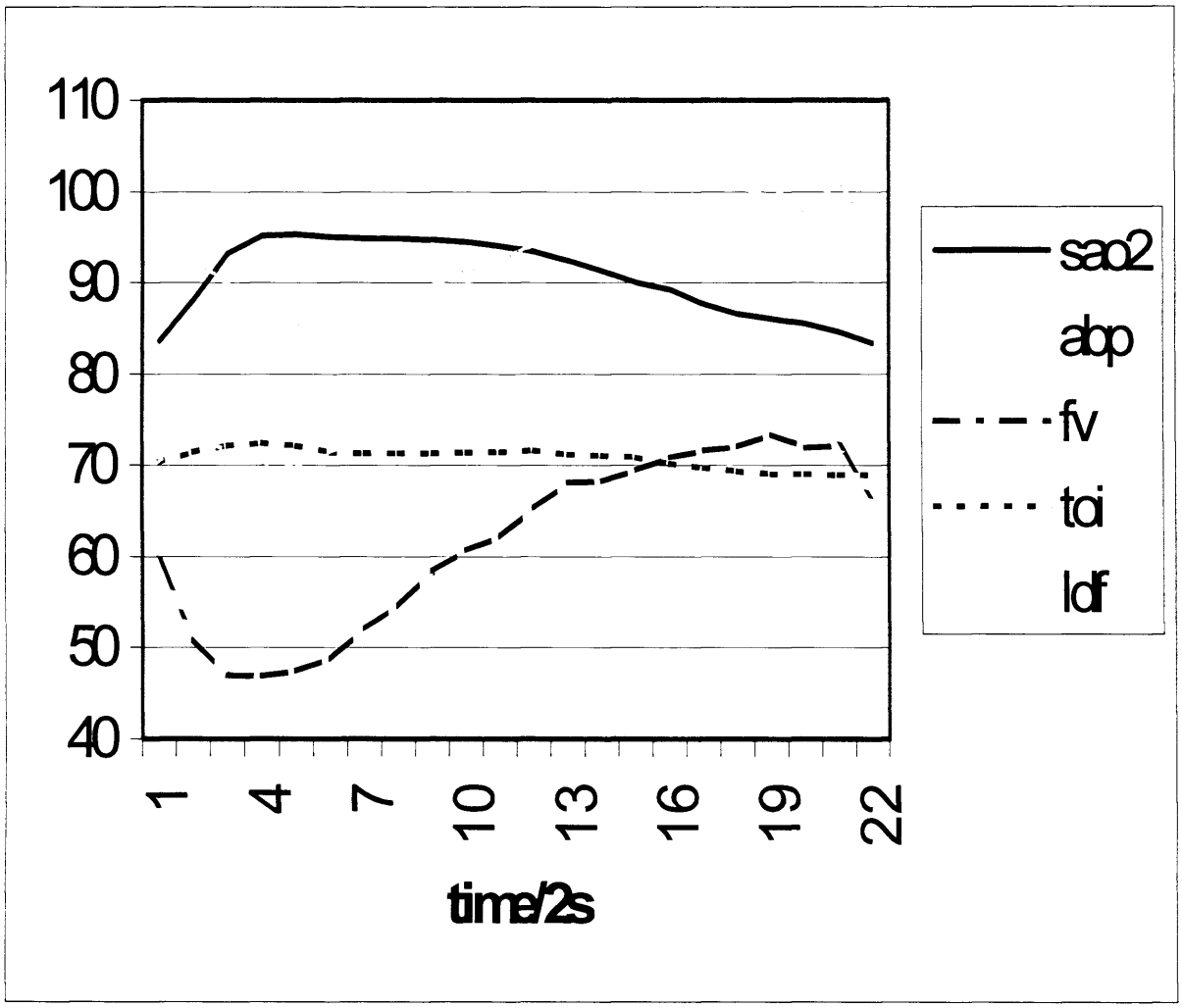


Figure 46. Cumulative average for subject 7 (16 apnoeas)

16 apnoeas averaged every 2s with minimum SaO_2 at time 0 to illustrate the temporal relationship of changes in different parameters. Satshift = arterial oxygen saturation, toi = tissue oxygenation index, fv = cerebral blood flow velocity, abp = (mean) arterial blood pressure, ldf = laser doppler flow. Units on the y axis are % for satshiftand % for TOI, m/s for fv, mmHg for abp, and arbitrary units for ldf. A finger oximeter was used in this subject because of poor recordings from the ear oximeter so saturation has been corrected for 20s timelag between finger and ear oximeter.

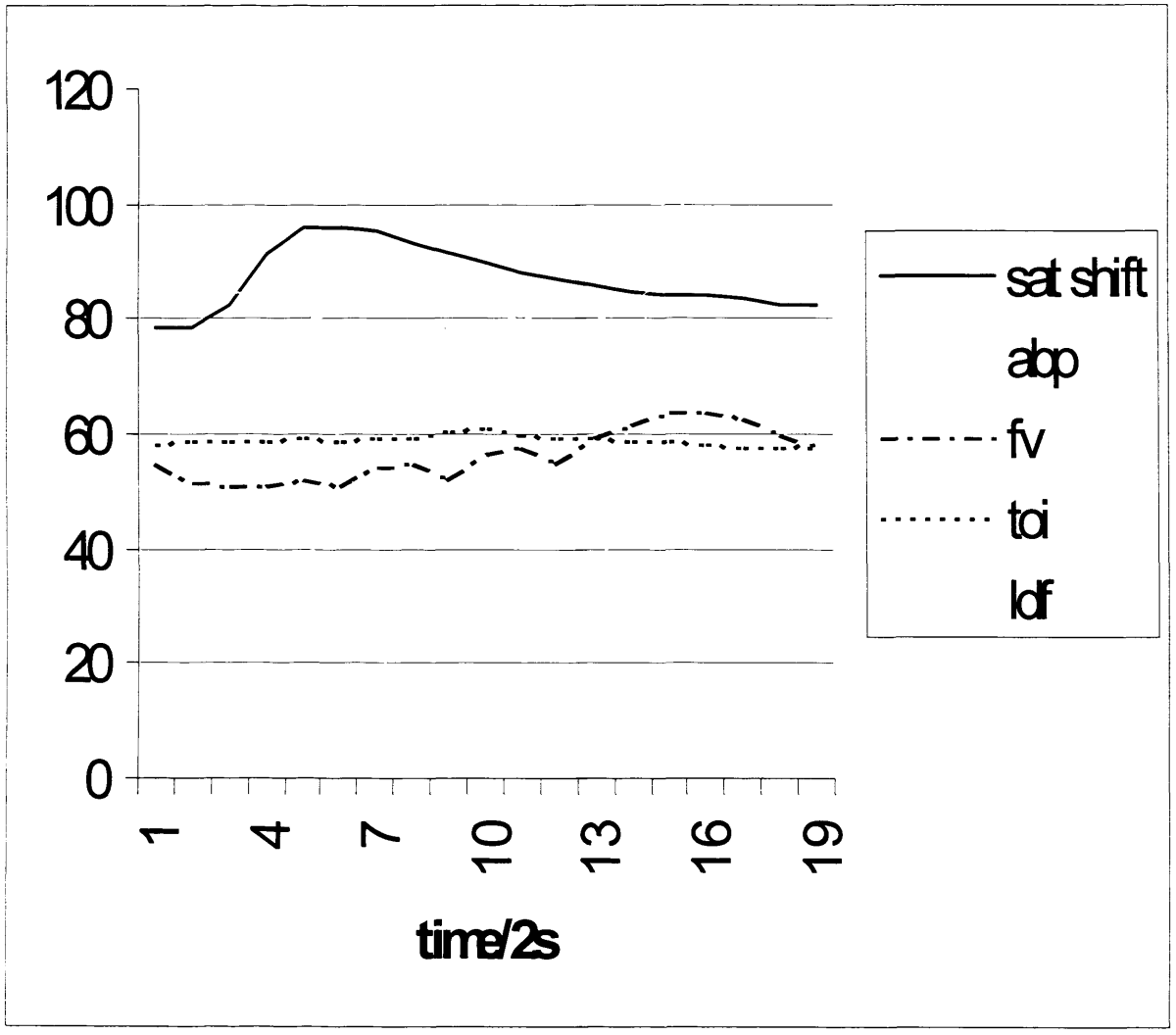
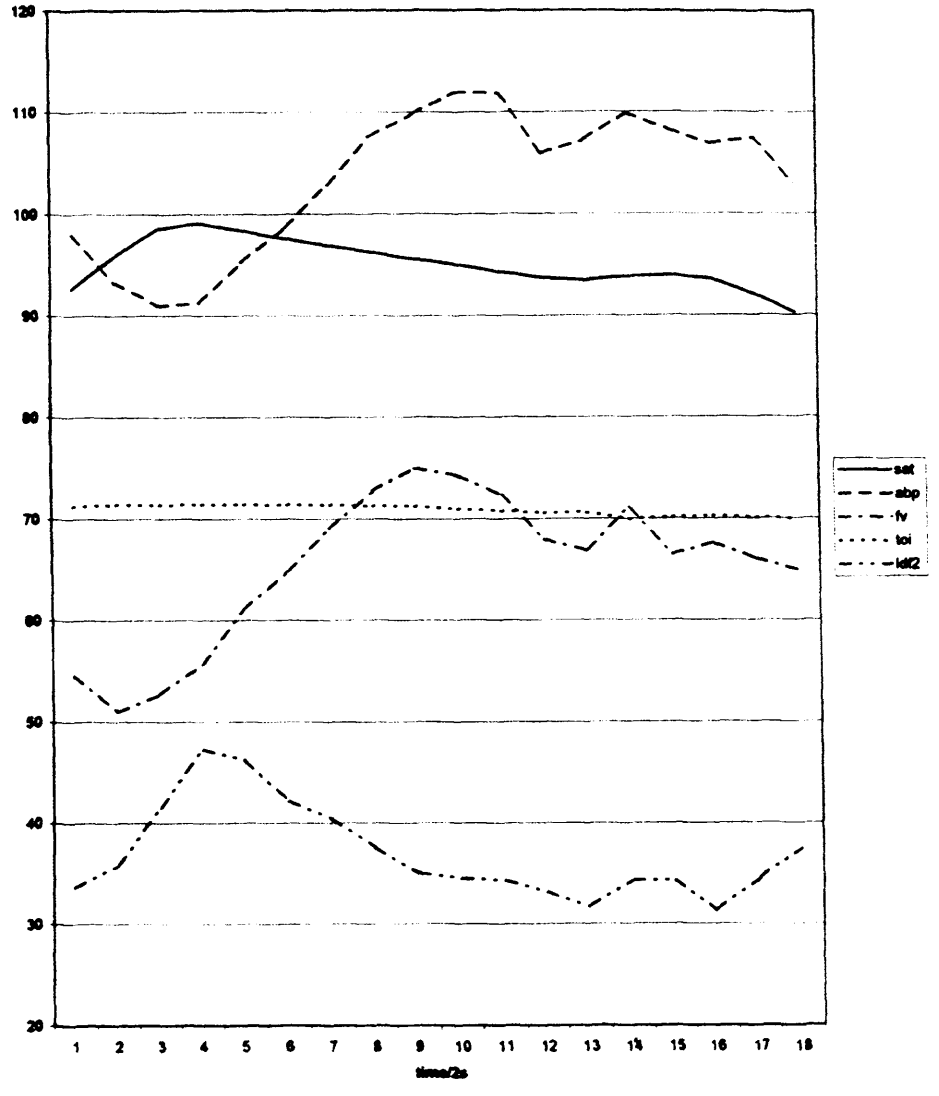


Figure 47. Cumulative average for subject 6 (15 apnoeas)

15 apnoeas averaged every 2s with minimum SaO_2 at time 0 to illustrate the temporal relationship of changes in different parameters. Sat = arterial oxygen saturation, toi = tissue oxygenation index, fv = cerebral blood flow velocity, abp = (mean) arterial blood pressure, ldf = laser doppler flow. Units on the y axis are % for sat and % for TOI, m/s for fv, mmHg for abp, and arbitrary units for ldf.



9.7.8 Subject 8 (CBFV changes without SaO_2 changes)

Data from subject 8 who had changes in CBFV without saturation changes were analysed separately. His raw data is shown in Fig 48. In 26 events the average change in ABP was 15.6+/- 3.6; in CBFV was 9.5 +/- 2.7, in SaO_2 was 0.8 +/- 0.7 and in TOI was 2.7 +/- 0.9.

Correlations between TOI difference and differences in SaO_2 and ABP were not significant; however correlation between magnitude of change in CBF and in TOI was significant (p=0.005, regression coefficient 1.52, 95%CI 0.51-2.54). Cumulative average is shown in Figure 49.

Figure 48. Raw data from subject 8 during period of repetitive change in CBFV

This illustrates the raw data output recorded every 2s. Abp = (mean) arterial blood pressure, fv = cerebral blood flow velocity, SaO_2 = arterial oxygen saturation, toi = tissue oxygenation index. Units on the y axis are mmHg for abp, m/s for fv, % for SaO_2 and % for TOI.

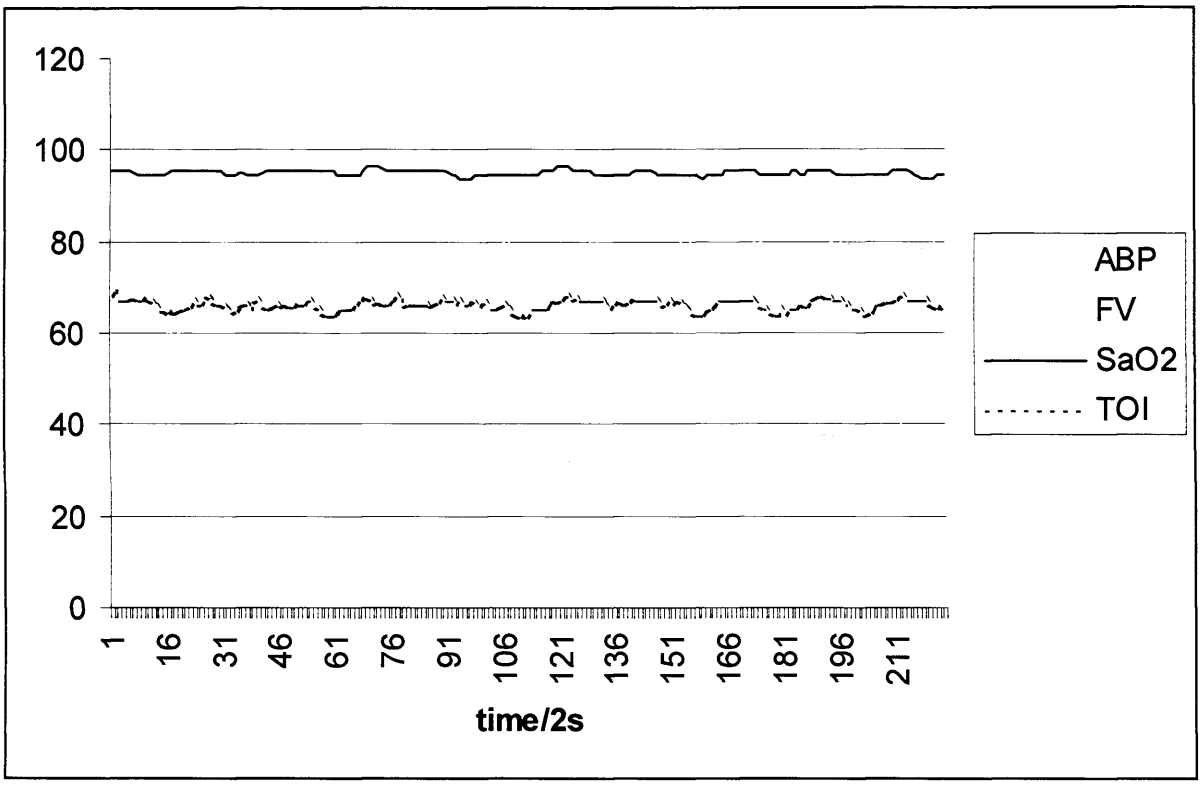
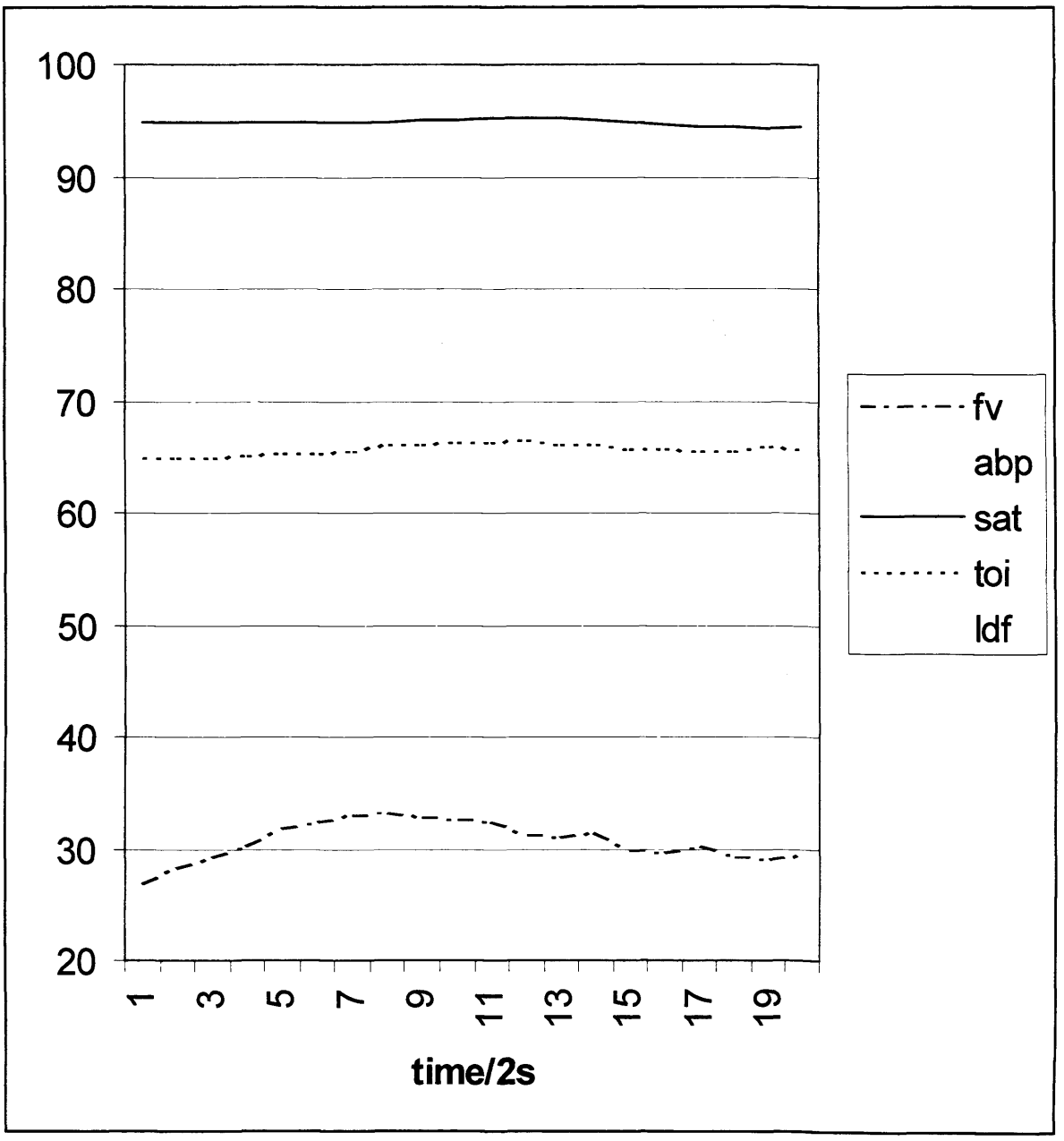


Figure 49. Cumulative average from subject 8 (15 episodes CBFV change)

15 episodes of CBFV (cerebral blood flow velocity) change averaged every 2s with minimum fv at time 0 to illustrate the temporal relationship of changes in different parameters. Abp = (mean) arterial blood pressure, fv = cerebral blood flow velocity, sat = arterial oxygen saturation, toi = tissue oxygenation index, ldf = laser Doppler flow. Units on the y axis are mmHg for abp, m/s for fv, % for SaO_2, % for TOI and arbitrary units for ldf.



9.8 CONCLUSIONS FROM THESE RESULTS

9.8.1 TOI changes are affected by changes both in cerebral blood flow and in arterial saturation.

TOI depends on both CBFV and SaO_2. We showed this in multiple regression in 7 subjects (287 apnoeas), and also in subject 8 where SaO_2 was effectively constant, changes in CBFV were associated with changes in TOI.

9.8.2 TOI changes are not affected by extracranial changes

Changes in arterial blood pressure will affect the extracranial circulation which can be assessed using laser Doppler flowmetry. Changes in cerebral blood flow should affect the intracranial circulation and it may be possible to assess this using TOI. The association between CBFV and ABP changes and the occurrence of both changes during apnoea means that it is difficult to demonstrate changes in TOI due to changes in CBFV independent of changes in ABP using crude measurements of maximum change during apnoea. Cumulative averaging suggests a closer temporal relationship between TOI changes and CBFV changes than ABP changes. In subject 8 correlations between TOI changes and ABP changes were not significant. There was no relation between LDF measurements and TOI measurements in subject 2. Our results do not rule out the high specificity of the NIRO 300 for intracranial changes previously found.

9.8.3 THB (relative cerebral blood volume) can not be used as a proxy for changes in CBFV, (as used in chapter 8).

These results suggest that the NIRO THb measurements are closely related to ABP measurements and so may reflect extracranial blood flow changes more than TOI does. The OHbratio measurement did not appear useful in explaining the physiology in this group. It aims to describe what fraction of the incoming blood during the CBF surge towards the end of apnoea is oxygenated, however it depends on the assumption that the change in THb comes from a change in CBF, which may not be the case. Also in the previous validation very low OHb ratios were reached by two subjects during REM sleep so the range was much higher.

9.8.4 Changes in cytochrome oxidase redox state during obstructive sleep apnoea are related to cerebral oxygenation measured independently of NIRS

Cytox measurements made in this validation study are similar to those made in the previous validation study. The associations found here between cytox changes and changes in CBFV and in SaO_2, support a real rather than artefactual explanation of the observed changes.

10. SUBJECTS AND PROTOCOLS FOR STUDY COMBINING NOCTURNAL NIRS MEASUREMENTS WITH OBJECTIVE NEUROPSYCHOLOGICAL TESTING

10.1 OVERALL HYPOTHESIS

Measurement of cerebral oxygenation using near-infra red spectroscopy gives more valid information than measurement of arterial oxygen saturation alone.
The hypothesis underlying the prospective trial protocol was that measurement of cerebral oxygenation using NIRS would be a better predictor of neuropsychological function than arterial saturation, but the neuropsychological results are not presented in this thesis.

10.2 INTRODUCTION

This thesis includes details of how the NIRO300 output was used to compare cerebral oxygenation between patients in a prospective study also using neuropsychological testing. Neuropsychological results are not included in this thesis. An outline of the study protocol is given here. The prospective study was entitled "Impact of obstructive sleep apnoea on cerebral oxygenation, measured by near-infrared spectroscopy, and the consequences for neuropsychological function" and the protocol was designed in collaboration with Prof S Newman and the Unit of Health Psychology at UCL between 1999 and 2000, while validation studies were taking place. This study assessed neuropsychological function, objective sleepiness, conventional polysomnographic measures of OSA severity, and

cerebral oxygenation using near infrared spectroscopy, in a group of patients with OSA before and after CPAP therapy, using a group of snorers as a comparison group for the neuropsychological tests.

10.2.1 Subject selection

Consecutive referrals to a sleep new patient clinic for possible obstructive sleep apnoea were recruited to the study, prior to any overnight sleep investigations. Inclusion criteria were all consenting subjects who were undergoing a screening sleep study for possible OSA because of snoring or daytime symptoms, irrespective of Epworth sleepiness score or reported snoring or witnessed apnoea. Referrals came for GPs, or other hospital specialties, mainly ENT or endocrinology. Exclusion criteria were cerebrovascular disease with residual disability, significant heart failure, significant chronic obstructive pulmonary disease, metabolic encephalopathy, untreated psychiatric disorder, insufficient command of the English language to perform the neuropsychiatric tests (which require literacy and verbal fluency), insufficient hearing or visual acuity for the neuropsychological tests.

10.2.2 Study visits

Visit 1 (DAYTIME)

All patients referred with suspected sleep apnoea were invited to attend a research clinic on a Thursday morning. At this clinic, following a routine history and examination, they were given information about the study, and were invited to consent to participate. Initial investigations (full blood count, thyroid function tests, spirometry, electrocardiogram, blood pressure) were performed at this stage.

Visit 2 (DAYTIME)

A neuropsychological assessment, using specially selected tests, were performed by a psychologist on all subjects, taking about 40minutes. Following this the subject had an Osler maintenance of wakefulness test performed supervised by the research fellow. They were asked to complete an Epworth Sleepiness Scale.

Visit 3 (OVERNIGHT)

A Visilab sleep study was carried out, in sleep study rooms at the Middlesex Hospital. This sleep study was analysed in the context of the clinical features to diagnose if the subject had obstructive sleep apnoea or was a simple snorer. Diagnosis of OSA was based on a dip rate >10, with confirmed apnoeas on video, and daytime symptoms. OSA

patients had a repeat visilab study on CPAP the following night to determine the effectiveness of CPAP in abolishing apnoeas.

Visit 4 (OVERNIGHT) (OSA ONLY)

Subjects with OSA were invited for an overnight polysomnography study with simultaneous NIRS (near infra red spectroscopy) measurements. The following morning each subject was shown how to use CPAP and loaned a CPAP machine, fitted with compliance monitoring.

Subjects were contacted weekly by telephone to check compliance, mask problems,etc.

Visit 5 (DAYTIME)

After 4 weeks OSA patients and snorers as a comparison group underwent repeat neuropsychological assessment, Osler maintenance of wakefulness test and Epworth Sleepiness Scale.

Visit 6 (OVERNIGHT) (OSA ONLY)

After 4 weeks of treatment subjects with OSA had a repeat polysomnography and NIRS measurements performed while using CPAP. CPAP compliance was recorded.

10.2.3 Osler Maintenance of Wakefulness test.

The Oxford sleep resistance test (Osler test, Stowood Scientific Instruments, Oxford, UK) (35) was chosen as the objective test for assessment of wakefulness in this study. It is a behavioural test, rather than being based on polysomnographic criteria of sleep onset, and is therefore simpler to administer and less operator dependent. The standard instructions are the same as a conventional maintenance of wakefulness test: the subject is asked to lie semirecumbent in a dark room and asked to remain awake. They are asked to press a switch (touch sensitive) in response to a small regularly illuminated light emitting diode lit for 1s every 3s. If there is no response for 7 illuminations (21s), the computer beeps and the test is ended. The test is terminated at 40mins if not asleep. Subjective sleepiness was also assessed using the Epworth Sleepiness score (36).

10.2.4 Neuropsychological testing

A battery of tests were selected by the Unit of Health Psychology, University College, London. Particular tests were selected because they examine the domains previously shown to be affected in OSA. I was not involved in the test selection or administration as

they were all administered by a trained psychologist from the Unit of Health Psychology, UCL.

10.2.5 CPAP machines

Pressure titration was performed manually followed by an in-patient night on CPAP with oximetry or visilab monitoring to ensure diprate correction. The machine used was the ResMed CPAP S6 which monitors compliance with a pressure sensor (mask on time), rather than just recording the hours the machine is switched on. Compliance was read on the day of the repeat neuropsychological tests to give total days of loan, average use in total, percentage of total days when machine used, and average use on usage days.

10.2.6 Analysis

Summary cerebral oxygenation measures were derived from the overnight recordings for use in regression analysis. Regression analysis was used to predict neuropsychological score pre treatment using age, education, sleepiness, AHI and cerebral oxygenation. Regression analysis was also employed to predict neuropsychological outcome post intervention using sleepiness, AHI and cerebral oxygenation as predictors. The derivation of summary measures is described in this thesis, but the results of neuropsychological testing are not.

The following tables (Tables 40-44) give descriptive data for each subject with OSA who was offered polysomnography with NIRO monitoring, including demographic and clinical data, sleepiness data, polysomnography data and compliance data.

Table 40. Demographic and descriptive data for subjects with OSA in prospective study

BMI = body mass index, f = female, all other subjects male.

Id number	*Age/yr*	*Smoke/day*	*Alcohol Units/week*	*Coffee Cups/day*	*Height /m*	*Weight /kg*	*BMI kg/m2*	*Collar size cm*	*Blood pressure mmHg*
1	59	3	50	1	1.8	81	25	-	140/92
2	54	Ex	3	0	1.66	87	31	17.5	120/70
3	55	Never	16	1	1.82	93	28	16.5	-
4	54	Ex	56	1	1.8	123	37	-	140/75
6 f	51	3	15	1	1.73	85	27	-	140/85
7	28	Never	-	0	1.75	135	44	-	140/95
8	43	Ex	0	8	1.79	86	42	17.5	130/80
14	31	Ex	1	0	1.84	109	32	-	140/90
16	44	Never	10	5	1.83	90	27	-	120/80
20	59	Never	0	2	1.69	85	30	16.5	120/80
21	48	Never	40	0	1.65	140	52	18.5	140/90
23	47	40	0	6	1.82	106	32	17	174/98
28	53	1	32	1	1.75	71	23	-	156/100
31	45	Never	0	3	1.73	114	38	18.5	132/89
35 f	51	17	0	0	1.57	81	33	16	138/78
38 f	55	Never	1	3	1.64	67	25	13	180/120
39	39	Ex	3	2	1.78	97	30	15.5	140/90
42	53	Ex	0	0	1.74	97	32	17	150/100
44	46	Never	1	0	1.64	72	26	16	190/130
47	43	Never	0	0	1.72	152	52	-	130/80
49	45	5	25	1	1.7	140	49	19	150/98
52	49	Never	2	0	1.72	94	32	17	130/80
54	71	Never	-	-	1.72	102	34	17.5	180/80
55	46	Never	14	-	1.86	127	37	18	130/100
60	41	30	0	30	1.76	86	28	15.5	120/70
63	64	Ex	-	0	1.68	89	25	18	130/80
68	32	6	10	0	1.76	93	30	16.5	125/88
69	49	Never	20	0	1.82	118	35	18.5	140/85
70	43	Never	4	3	1.73	103	34	18.5	130/90
72	64	Never	20	2	1.69	73	25	16	150/70
75	51	Never	1	3	1.9	113	31	17	140/95
79	44	Ex	15	-	1.72	97	33	17	150/95
81	47	Never	7	5	1.84	114	33	16.5	140/100
84 f	48	Ex	21	0	1.64	95	35	18	140/90
86	59	Current	2	0	1.69	96	34	17.5	130/80
87 f	45	Ex	2	3	1.63	139	53	18	-
88	50	Ex	5	2	1.77	116	39	18	120/85
89	64	Ex	25	6	1.66	91	33	17.5	146/84
93	69	Never	4	-	1.76	93	30	16.5	140/90
95	50	Never	7	1	1.78	146	46	20	150/100
96	43	Never	2	0	1.96	196	51	19	140/90
97	31	Ex	35	-	1.79	110	34	17	130/80
98	40	Never	-	2	1.82	146	45	19	140/85
101	60	30	0	6	1.72	121	41	17	140/88
102	56	Ex	14	4	1.83	98	29	17.5	125/85
106	45	Ex	2	1	1.78	99	33	17	130/80
111	33	20	0	0	1.78	109	34	17	-
114	65	Never	0	1	1.65	72	27	13.5	130/80
118	29	Never	6	0	1.84	119	35	-	120/84
119	39	Never	2	6	1.78	85	27	-	138/80
122	52	20	16	6	1.87	107	30	17.5	140/85
123	49	Never	8	1	1.79	115	35	17.5	130/95
125	35	Ex	2	1	1.77	120	38	17.5	160/90
126 f	52	Ex	36	0	1.68	94	33	17.5	125/85
127	65	Never	10	2	1.71	95	32	18	-
129	62	Never	4	0	1.84	103	30	17	130/80
130	47	Current	0	1	1.67	119	42	17.5	150/100
135	58	never	20	0	1.76	91	29	16	150/90

Table 41. Presenting symptoms and comorbidities (Total n=58, all OSA subjects)

Symptom or comorbidity	*Number with symptom/comorbidity*	*Percentage*
Snoring	57	98%
Witnessed apnoea	45	78%
Sleepiness	50	86%
Cerebrovascular disease	1	
Cardiovascular disease	9	16%
Respiratory disease	8	15%
Hypertension	23	40%
Psychiatric history	9	16%
Endocrine history	4	9%
On medication	29	50%

Table 42. Spirometry, screening dip rate and sleepiness variables pre and post CPAP for OSA patients in study

FEV1 = forced expiratory volume in first second, FVC = forced vital capacity, ESS = Epworth sleepiness score. Osler = mean of 2 runs of Osler sleep resistance test.

Id number	*FEV1 /l*	*FVC /l*	*ESS pre CPAP*	*Osler pre CPAP min*	*Screening dip rate /hour*	*ESS post CPAP*	*Osler post CPAP min*
1	4.56	6.12	15	29.7	11	5	40
2	1.78	2.27	20	3.5	40	13	4.6
3	3.95	5.3	14	4.0	21.6	17	10.7
4	2.76	3.6	15	38.1	31	11	40
6 f	3.17	3.72	7	13.6	13	7	9.7
7	3.58	3.97	20	10.0	.	18	28.8
8	4.22	4.95	11	26.6	56	10	32.3
14	3.97	4.85	16	12.8	24	13	32.2
16	3.87	4.96	16	27.0	22	11	23.2
20	2.13	2.52	19	5.9	60	7	40
21	1.72	2.17	18	5.7	78	20	39.7
23	2.93	3.32	10	14.6	66.7	13	14.8
28	2.41	3.13	20	5.9	13	16	36.8
31	2.42	4.45	8	14.6	14	5	27.9
35 f	2.08	2.53	17	26.2	31.4	21	15.2
38 f	2.49	2.74	18	14.9	6.9	15	40
39	3.87	4.42	13	10.7	34	9	40
42	2.28	4.32	14	40	16	3	22.1
44	2.76	3.33	12	27.4	29.6	.	40
47	1.98	2.92	13	23.0	113	11	31.2
49	2.41	3.11	18	14.0	46.2	22	.
52	3.16	4.31	13	28.8	12	14	28.9
54	3.06	3.99	9	40	43.5	8	40
55	3.61	4.44	12	8.1	66.5	18	17.0
60	3.44	4.16	12	4.4	13	11	6
63	2.59	2.8	7	8.4	17	6	19.0
68	2.99	3.02	10	21.2	27	16	16.3
69	2.27	2.94	4	40	35	5	40
70	3.74	3.75	18	4.1	57.4	15	11.7
72	3.02	3.59	5	34.8	26	6	40
75	2.66	2.77	7	13.2	.	9	24.2
79	3.16	3.63	6	9.0	86	0	10.8
81	3.05	3.74	17	28.0	38.7	21	7.2
84 f	2.41	2.72	12	12.1	10.4	9	40
86	.	.	12	10.7	42.8	5	25.1
87 f	1.96	2.38	20	2.1	133	16	13.0
88	2	2.52	16	5.4	34.3	17	20.8
89	1.99	2.31	15	10.1	58	17	9.4
93	3.36	4.5	15	7.6	28.4	10	40
95	3.94	4.83	8	40	1.5	8	40
96	3.22	3.66	7	32.7	79.6	6	40
97	1.48	5.35	3	40	36	6	40
98	3.59	4.09	16	38.8	13	3	38.9
101	1.76	1.88	13	10.9	76.1	10	.
102	2.03	4.15	16	11.8	54.4	15	22.9
106	3.3	3.97	11	28.2	12.5	11	12.0
111	3.22	3.77	2	28.9	13	12	23.9
114	2.19	2.51	11	40	11.4	17	22.0
118	2.94	4.119	11	20.4	18.7	6	40
119	2.87	3.09	12	25.2	49.5	13	.
122	3.86	4.55	17	35.5	16.6	15	39.6
123	3.4	3.74	16	25.6	51.2	6	40
125	2.95	3.15	6	28.0	27.6	13	8.7
126 f	3.81	4.09	6	40	17	10	40
127	2.68	2.68	9	36.7	35.6	4	40
129	2.87	4.21	19	14.6	32.3	9	32.7
130	1.85	2.01	9	2.6	39.4	8	25.3
135	2.81	3.03	.	29.7	11.9	8	40

Table 43. Polysomnographic data for OSA patients

CPAP= continuous positive airway pressure, AI= arousal index, AHI = apnoea hypopnoea index, REM = rapid eye movement

Id number	*Pre CPAP sleeptime /min*	*Pre CPAP REM duration /min*	*Pre cpap AI /hr*	*Pre CPAP AHI /hr*	*Post CPAP sleep time/mins*	*Post CPAP REM duration/min*	*Post CPAP AI /hr*	*Post CPAP AHI /hr*
1	246.3	29.3	45.1	49.4	413.3	72.7	7.1	4.5
2	354	31.7	36.6	43.4	329.3	73.7	15.5	6
3	474.3	68	22.8	26.3	503.7	104	4.8	.5
4	420	43.3	21.1	26.9	191.3	41.3	13.8	6.9
6 f	417	54.3	11.1	3.7	456	97.3	5.9	.7
7	562	4.7	26.9	85	430.7	97	7.5	3.3
8	352.7	29.3	31.8	66.6	.	.	.	.
14	289.7	39.7	59.2	70	340.3	41.7	18	10.4
16	378.7	74.3	18.4	23.9	.	.	.	.
20	288.7	13	47.2	73.2	339.7	57.7	7.4	7.4
21	374.7	29.7	62.3	81	303	78.5	5.1	4.3
23	248.7	2	22.2	54	463.3	64.3	14.6	23.4
28	375	45.7	35.7	34.4	267.7	40.7	15.5	1.8
31	357	53.3	17.1	10.6	.	.	.	.
35 f	320.3	32.3	31.8	16.5	279.7	64.3	17.2	10.7
38 f	373.3	21.7	19.6	17.5	.	.	.	.
39	344.7	36.7	50.5	61.7	456.3	95	16.6	1.6
42	382.7	31	19.8	33.9	388	90.3	14.5	7.9
44	457.3	71	18.9	46.4	327.3	68.7	5.1	2.9
47	450	24	88.4	105.7	455.7	56	19.7	18.1
49	356.7	54	12.4	28.9	457.7	86	10.1	15.7
52	410.7	47.7	28.9	23.2	422	64.7	14.4	2
54	422.7	9.3	20	79.7	433.3	43.7	9.7	3.2
55	456.7	27	43.1	67	407.3	73.3	7.2	2.4
60	525.3	88.3	14.6	17.4	516.3	60.3	7.6	6.4
63	381.7	52.7	21.9	14.1	366.7	38.3	13.4	10.9
68	422	.3	45	86.3	448.3	78	23	24.5
69	349	17	59.5	54.5	344.7	38.3	29.6	5.2
70	416.7	33.7	26.2	62.2	417	38.3	9.4	8.8
72	389.7	34.3	21.6	63	355.7	61	8.5	2
75	421.3	33.3	26.1	35.2	399.7	76	4.3	1.1
79	400.7	55.7	50	82.7	438.3	88.3	7.4	2.3
81	390.7	50	21.3	79.9	529.7	108.3	6.9	8.6
84 f	297	35.3	21.4	12.1	312.7	59	13.2	3.3
86	341.7	7.7	16	15.5	337.3	36.7	6.4	1.4
87 f	418.7	9	20.2	106.4	415	121	4.2	13.6
88	275.3	5	39.2	22.4	357	44.7	6.4	1
89	473	100.7	28.9	70.9	.	.	.	.
93	429	75	13.7	20.6	384	81.7	6.7	3.8
95	360.7	9.3	10.6	15.5	.	.	.	.
96	402.7	13	41.4	78.1	350.3	56	14.7	32.5
97	418.7	70.3	18.6	41	488.3	106.7	9.7	5.2
98	453.3	54	10.5	20.2	242.3	12	3.7	5.7
101	343.7	20.7	31.3	25.1	.	.	.	.
102	452.3	16.3	30.2	62.3	467	140	9.4	5.3
106	378.7	16	7.6	13.2	429.3	63.3	1.3	5.7
111	455.7	64	11.9	30.4	520	88	3.5	.5
114	390.7	44	6.5	4.6	356.3	1.3	4.2	0
118	263	13	21.2	35.5	462.8	58.7	8.6	5.3
119	319.7	15	46.5	46.9	347.7	93.3	3.6	5
122	388	49.3	38.2	43.3	418	68.7	15.2	2.9
123	475	39	29.8	73.8	420.3	66.7	5.1	5.9
125	413	42	29.2	42.1	459.3	103.7	3.9	9.4
126 f	468.7	5.3	36.4	41	487.7	52.7	25.6	13.4
127	368	36	16.6	30.1	513.3	106	2.3	.2
129	355	29	19.4	39.7	420	54	3	1.3
130	420	47.3	14.3	23.1	306.7	59.7	4.3	3.1
135	179	0	13.7	49.2	.	.	.	.

Table 44. CPAP compliance data for OSA patients.

Subjects 8,31,38,87,95 and 135 refused to take CPAP following their initial trial night

Id number	*Days of CPAP use*	*Median use total nights, min*	*Percentage usage nights*	*Median use, usage nights, min*	*Use on night before poly, mins*
1	69	168	68.1	192	408
2	42	0	35.7	84	0
3	38	324	89.5	342	270
4	34	150	67.6	210	228
6 f	50	180	78	234	354
7	30	519	100	519	336
8	0	.	.	.	.
14	41	96	51.2	276	300
16	69	276	89.9	291	402
20	47	300	100	300	.
21	56	225	89.3	252	474
23	102	0	17.6	219	0
28	34	306	94.1	315	348
31	0	.	.	.	.
35 f	29	0	10.3	48	0
38 f	0	.	.	.	.
39	112	132	54.5	288	414
42	47	426	97.9	429	384
44	40	375	80	402	420
47	55	210	98.2	213	132
49	33	228	90.9	258	138
52	41	216	61	288	342
54	49	126	69.4	186	216
55	68	210	91.2	228	282
60	42	195	69	282	324
63	40	0	40	210	42
68	42	303	64.3	360	498
69	35	546	100	546	576
70	63	132	61.9	198	0
72	37	324	73	348	354
75	36	279	100	279	132
79	39	408	94.9	408	342
81	44	444	65.9	516	672
84 f	35	282	88.6	288	492
86	37	276	83.8	324	414
87 f	37	.	.	.	.
88	37	216	89.2	222	0
89	35	0	17.1	102	150
93	37	360	100	360	348
95	0	.	.	.	.
96	30	75	83.3	90	276
97	51	0	37.3	72	30
98	42	0	9.5	120	168
101	11	474	90.9	483	492
102	44	42	54.5	159	222
106	44	0	31.8	291	0
111	43	180	74.4	273	300
114	32	39	50	249	0
118	30	90	83.3	108	0
119	42	0	4.8	222	0
122	34	354	97.1	354	456
123	56	273	92.9	279	354
125	37	222	89.2	222	0
126 f	37	0	35.1	324	60
127	37	396	100	396	378
129	35	366	100	366	378
130	37	228	100	228	168
135	0	.	.	.	.

11. CALCULATION OF SUMMARY TOI MEASURES TO COMPARE SUBJECTS

11.1 OVERALL HYPOTHESIS

11.1.1 Measurement of cerebral oxygenation using near-infra red spectroscopy gives more valid information than measurement of arterial oxygen saturation alone

11.2 HYPOTHESES UNDERLYING ANALYSIS IN THIS CHAPTER

11.2.1 It is possible to use NIR cerebral oxygenation monitoring in unmanned full night polysomnography.

11.2.2 Summary measures from an overnight study can be calculated for TOI which differ from measures based on SaO_2 and conventional polysomnography measures.

11.3 INTRODUCTION

We have shown that TOI can be used to measure cerebral oxygenation in subjects with OSA, and that it adds additional information that cannot be predicted from simple arterial

oximetry and also reflects changes in cerebral blood flow. We then wanted to physiologically validate this new measurement to see if it was a better predictor of daytime neuropsychological function than conventional polysomnography variables. In order to do this we had to derive a summary measure of TOI from an overnight study that could then be used in analysis as a predictor of neuropsychological function. The summary measures used were area under the curve measures and dip rates derived as described in chapter 5. The main findings of the neuropsychology study are not presented in this thesis. In this chapter we describe the TOI AUC and dip rate measures and compare them with AHI and SaO_2 variables. We have seen how saturation and TOI are related at the level of individual apnoeas, but here the two are compared during overnight studies using exactly the same way of analyzing the two traces, to confirm whether different information is obtained. AHI is the gold standard measure for assessing OSA severity and so any new overnight measure of OSA severity is conventionally "validated" against AHI. Clearly validation against symptoms would be more physiological, but is not conventionally used. The results in this chapter therefore tabulate and describe overnight summary measures for TOI and relate them to similarly calculated saturation measures and conventional polysomnography variables.

11.4 SUBJECTS AND BASELINE CHARACTERISTICS

136 consecutive subjects were recruited from a clinic seeing referrals of subjects with possible obstructive sleep apnoea. Following a screening sleep study, 69 subjects (61 men) fulfilled criteria for polysomnography (4% oxygen desaturation dip rate >10 and obstructive apnoeas on video). Their mean (SD) age was 48.7yrs, (10.5), mean BMI 34.4 (7.2) kg/m^2, mean dip rate 36.2 (25)/hr, mean ESS 12.6 (4.8) and mean Osler sleep latency 20.3 (12.5) mins. 62 of 69 eligible patients underwent polysomnography, and the data obtained was adequate in 59 for AUC measurements, and 56 for dip rate measurements. 51 underwent repeat polysomnography after approx 1 month's treatment. Demographic, clinical and polysomnography data for these subjects are given in tables 40-44 in chapter 10.

We recorded full polysomnography with TOI monitoring onto the polysomnography computer, and we also recorded a digital output of TOI and SaO_2 onto a separate computer. This enabled us to calculate dip rates and AUC measurements using the same method for both TOI and SaO_2 as described in chapter 5. Anyone with experience of sleep medicine has a pretty good feel of how severe a subject is from isolated values of dip rate, AHI or T90, but when a new method like AUC is used, values even for SaO_2 need to be first described, then put into context by comparison with the familiar AHI values. Similarly dip rate and AUC values for TOI need to be described and compared to give the investigator a feel for their distribution and how they differ from the SaO_2 values.

The following tables include a description of the values obtained for TOI AUC and dip rate calculations, comparison of AUC values before and after treatment with CPAP, and relationship between these measures and the conventional poly measures: AHI, AI and mean minimum saturation. AUC measures include both the percentage of observations below a particular saturation (analogous to T90 as a fraction of total recording time) and the summated area below a particular saturation. The "percentage obs" measures thus measure fractional time spent below a particular saturation, whereas the "area under the curve" measures include both time and severity of desaturation.

11.4.1 Statistics

Calculated summary measurements are described using mean and SD. They are compared pre and post CPAP using a paired t test. The new measurements are compared to conventional polysomnographic measurements using correlation coefficients, using tables to give the significance level for a specified number of subjects (Biometrika ref). $P<0.05$ was taken as significant. Because of multiple comparisons $p<0.01$ is a more valid test of significance, and both are quoted.

11.5 AREA UNDER THE CURVE MEASUREMENTS AT BASELINE

Table 45 illustrates AUC measurements for SaO_2 and TOI at baseline. Although individuals may have very similar baseline maximum levels for SaO_2, baseline values for TOI are variable, and so AUC is expressed from a particular value (2%, 4% and 10% below baseline) rather than from an absolute saturation value. For example a subject might have a maximum SaO_2 of 100% so that nearly 100% of the observations (obs) were below 100%, 80% below 98%, 50% below 96% and 2% below 90%. This subject would have a "% obs 2% below maximum" of 80%, "% obs 4% below maximum" of 50%, and "% obs 10% below maximum" of 2%. For SaO_2 the "% observations 10% below maximum" is analogous to T90 (time below SaO_2 of 90%) divided by total time. Units for AUC are % per minute. If TOI and SaO_2 are compared, the % obs values tend to be higher for TOI, but the AUC values are very similar. Total AUC averages 421.5 %/min for SaO_2 and 415.5 %/min for TOI. AUC 10% below maximum averages 85.8%/min for SaO_2 and 50.8%/min for TOI.

Table 45. Mean values obtained for SaO_2 AUC variables before CPAP treatment (n=59).

SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, AUC = area under the curve (variation below maximum), maximum defined as value of SaO_2 or TOI that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are quoted here. Units for AUC are %/min.

	SaO_2				TOI			
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max
%observations 2% below maximum	90.9	7.2	68.4	98.6	94.0	4.4	77.9	98.7
%observations 4% below maximum	67.3	20.8	14	95.6	76.7	17.2	23.2	97.6
%observations 10% below maximum	18.7	20.5	0	72.1	23.1	22.7	0	87.2
AUC below maximum	421.5	231.9	173	1202	415.5	154.0	167	775
AUC 2% below maximum	307.7	231.5	72	1070	311.6	155.5	75	672
AUC 4% below maximum	213.6	221.3	6	966	210.2	144.1	17	559
AUC 10% below maximum	85.8	153.4	0	699	50.8	69.9	0	256

11.6 AREA UNDER THE CURVE MEASUREMENTS USING CPAP

We would expect AHI values on CPAP to be reduced to below 10, especially when CPAP studies are performed after a month of CPAP use at home so that poorly compliant subjects are likely to have stopped CPAP use. We might therefore predict that AUC levels would be reduced to a uniform low level. Following CPAP, AUC values are reduced, but maybe less than might be expected due to the sensitivity of this method and the noise in the traces (Table 46). "Mean AUC below maximum" on CPAP was 308.5 %/min for SaO_2 and 339.4 for TOI. "Mean AUC 10% below maximum" was 37.8 for SaO_2 and 10.5 for TOI. Apart from the "AUC 10% below maximum" the TOI values are higher than the SaO_2 values, suggesting that CPAP may correct SaO_2 better than cerebral oxygenation. Dips in SaO_2 are known to be greater in general than TOI dips during an apnea (ie TOI ranges are smaller), which accounts for the reduction in the AUC 10% below maximum for TOI.

Table 46. Mean values obtained for SaO_2 and TOI AUC variables using CPAP treatment (n=51).

SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, AUC = area under the curve (variation below maximum), maximum defined as value of SaO_2 or TOI that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are quoted here. Units for AUC are %/min.

	SaO_2				TOI			
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max
%observations 2% below maximum	86.9	12.8	46.9	97.8	93.7	4.2	81.1	98.5
%observations 4% below maximum	52.5	28.6	0.5	95	72.6	16.1	19.4	96.4
%observations 10% below maximum	8.1	14.0	0	70.1	9.8	12.4	0	68
AUC below maximum	308.5	170.2	89	944	339.4	89.7	161	675
AUC 2% below maximum	193.7	165.1	3	804	231.7	86.1	69	541
AUC 4% below maximum	114.5	148.4	0	707	134.1	78.0	19	442
AUC 10% below maximum	37.8	88.2	0	412	10.5	20.4	0	131

11.7 DIP RATE VARIABLES PRE TREATMENT

Apnea associated dip rates were calculated using the polysomnography software as described in chapter 5 for SaO_2 and TOI. As smaller dips were observed for TOI than for SaO_2, both 2% and 4% dip rates were calculated for TOI.

Mean 4% SaO_2 dip rate was 32.6. Mean 2% TOI dip rate was 38.1 and mean 4% TOI dip rate was 24, so that mean 4% SaO_2 diprate was between the 2% and 4% TOI diprate.

Mean apnoea associated diprates overall and in REM were similar (Table 37). To ensure that dip rate calculations were objective and without bias they were calculated using the polysomnography software algorithm only, without subsequent manual revision and allocation of "unsures". Unfortunately this meant that TOI diprates could not be calculated for the polysomnography on CPAP because the analysis program was not able to

distinguish correctly between loss of mask contact and apnoea (because the airflow probe was attached to the CPAP mask).

Table 47. Mean and range of dip rate variables for pre-treatment polysomnography for SaO_2 and TOI.

SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, REM =rapid eye movement sleep. Units for AUC are %/min. Units for dip rates are /hr.

Variable	Number	Mean	SD	Minimum	Maximum
4% SaO_2 diprate	56	32.6	23.7	1.5	90.6
4% SaO_2 dip rate (REM)	46	32.9	27.1	0	88.0
2% TOI dip rate	56	38.1	24.4	2.6	97.6
4% TOI dip rate	56	24.0	23.2	0.1	95.7
2% TOI dip rate (REM)	46	36.5	27.2	0	90
4% TOI dip rate (REM)	46	25.0	23.6	0	86.0

11.8 COMPARISON BETWEEN VARIABLES BEFORE AND AFTER CPAP

The following table compares values of AUC and dip rate and conventional polysomnography variables on and off CPAP using a Wilcoxon rank test. Apart from baseline TOI and sat; AUC variables for both TOI and saturation, and conventional polysomnography variables significantly improved on CPAP, as would be expected (Table 48).

Table 48. Comparison between pairs of variables with and without CPAP.

sat = arterial oxygen saturation, TOI = tissue oxygenation index, AUC = area under the curve (variation below maximum), maximum defined as value of SaO_2 or TOI that 99% of observations are below. Mean values of AUC below maximum (0) and below three thresholds (2%, 4% and 10%) below maximum are quoted here. Ranges for these means are given in table 45. Units for AUC are %/min. CPAP = continuous positive airway pressure treatment. AHI = apnoea hypopnoea index, mean min SaO_2 = mean of minimum values during apnoeas, REM = rapid eye movement. Statistical test is Wilcoxon rank sum, assuming unequal variances.

.

Variable	number	Pre-CPAP	On CPAP	pvalue (Wilcoxon rank test)
AUC 0 toi	49	420.2	337.1	0.0014
AUC 2 toi	49	316.8	229.5	0.0008
AUC 4 toi	49	214.6	132.0	0.0005
AUC10 toi	49	49.1	10.0	0.0001
AUC 0 sat	49	438.7	309.0	0.0000
AUC 2 sat	49	324.6	194.3	0.0000
AUC4 sat	49	229.5	114.3	0.0000
AUC 10 sat	49	99.7	37.0	0.0001
Baseline sat (%)	49	99.3	99.4	0.98
Baseline toi (%)	49	76.4	78.4	0.11
Arousal index /hr	51	29.4	10.1	0.0000
AHI /hr	51	45.7	6.5	0.0000
Mean min SaO_2 %	47	88.2	93.6	0.0000
Mean dip SaO_2 %	49	9.42	5.03	0.0000
REM AHI /hr	48	36.0	7.4	0.0000

11.9 RELATIONSHIP BETWEEN CONVENTIONAL POLY VARIABLES AND AUC VARIABLES PRE TREATMENT

New sleep study variables may be validated as measures of OSA severity by comparison with AHI. AUC variables for SaO_2 were significantly associated with conventional

polysomnography variables. The variable: "% obs 10% below maximum" (analogous to T90) and all the AUC variables were strongly related to the conventional saturation variables (Table 49). Relationships with AHI were less strong. This would be expected as AUC variables and conventional saturation variables are based on the pulse oximeter readout. The poorer correlations with the "% obs below maximum" than with AUC reflect the fact that AUC measures include the severity of desaturation as well as its duration.

Table 49. Correlation coefficients for relationship between poly variables and AUC variables for SaO_2 from baseline pretreatment polysomnography (n=57)

AUC = area under the curve (variation below maximum), maximum defined as value of SaO_2 that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are compared here. AHI = apnoea hypopnoea index, mean min SaO_2 = mean of minimum values during apnoeas, mean sat dip = mean of SaO_2 drops during apnoea.

	AHI	Mean min SaO_2	Mean sat dip
%observations 2% below maximum	0.181ns	-0.421**	0.367**
%observations 4% below maximum	0.380**	-0.496**	0.484**
%observations 10% below maximum	0.642**	-0.814**	0.825**
AUC below maximum	0.617**	-0.833**	0.856**
AUC 2% below maximum	0.620**	-0.834**	0.852**
AUC 4% below maximum	0.622**	-0.840**	0.861**
AUC 10% below maximum	0.582**	-0.835**	0.867**

** $p<0.01$

TOI AUC variables were weakly correlated with AHI, but not significantly related to conventional oxygen measures (Table 50). This is expected as TOI variables are produced from a different trace to the oxygen measures, and so best correlation is with the AHI or event rate. This does suggest that TOI and SaO_2 measure different things, but also that there is some relation between TOI measures and OSA severity.

Table 50. Correlation coefficients for relationship between poly variables and AUC variables for TOI from baseline pretreatment polysomnography (n=57)

AUC = area under the curve (variation below maximum), maximum defined as value of TOI that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are compared here. AHI = apnoea hypopnoea index, mean min SaO_2 = mean of minimum values during apnoeas, mean SaO_2 dip = mean of SaO_2 drops during apnoea.

	AHI	Mean min SaO_2	Mean SaO_2 dip
%observations 2% below maximum	0.044	0.048	-0.160
%observations 4% below maximum	0.211	-0.088	0.031
%observations 10% below maximum	0.324*	-0.260	0.216
AUC below maximum	0.316*	-0.251	0.193
AUC 2% below maximum	0.302*	-0.223	0.174
AUC 4% below maximum	0.305*	-0.235	0.186
AUC 10% below maximum	0.258	-0.259	0.205

** $p<0.01$,* $p<0.05$

11.10 RELATIONSHIP BETWEEN CONVENTIONAL POLY VARIABLES AND AUC VARIABLES POST TREATMENT

The relationships between AUC variables and polysomnography variables were also examined in the studies on CPAP. On CPAP the relationship between the SaO_2 AUC variables and conventional poly variables was less strong presumably because most SaO_2 variation was not now caused by apnoeas or hypopnoeas (Table 51). There was no significant correlation with AHI, but reasonable correlations (0.396 – 0.758) with the saturation variables.

Table 51. Correlation coefficients between poly variables and AUC variables for SaO_2 from post treatment polysomnography (n=47)

AUC = area under the curve (variation below maximum), maximum defined as value of SaO_2 that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are compared here. AHI = apnoea hypopnoea index, mean min SaO_2 = mean of minimum values during apnoeas, mean SaO_2 dip = mean of SaO_2 drops during apnoea.

	AHI	Mean min SaO_2	Mean SaO_2 dip
%observations 2% below maximum	0.074	-0.395**	0.246
%observations 4% below maximum	0.183	-0.542**	0.480**
%observations 10% below maximum	0.094	-0.742**	0.522**
AUC below maximum	0.086	-0.737**	0.494**
AUC 2% below maximum	0.092	-0.748**	0.500**
AUC 4% below maximum	0.073	-0.758**	0.476**
AUC 10% below maximum	-0.018	-0.674**	0.332*

** $p<0.01$, * $p<0.05$

There were no significant correlations on CPAP between TOI AUC measures and conventional poly variables (Table 52). As even without CPAP the only relationship was with AHI, this again suggests that most of the TOI variation on CPAP was not related to OSA.

Table 52. Correlation coefficients for relationship between poly variables and AUC variables for TOI from post treatment polysomnography (n=47)

AUC = area under the curve (variation below maximum), maximum defined as value of TOI that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are compared here. AHI = apnoea hypopnoea index, mean min SaO_2 = mean of minimum values during apnoeas, mean SaO_2 dip = mean of SaO_2 drops during apnoea.

	AHI	Mean min SaO_2	Mean SaO_2 dip
%observations 2% below maximum	0.176	0.075	0.091
%observations 4% below maximum	0.156	0.044	0.107
%observations 10% below maximum	0.119	-0.032	0.077
AUC below maximum	0.140	0.038	0.123
AUC 2% below maximum	0.110	0.006	0.113
AUC 4% below maximum	0.093	0.033	0.102
AUC 10% below maximum	0.071	0.012	0.058

** $p<0.01$

11.11 RELATIONSHIP BETWEEN CONVENTIONAL POLY VARIABLES AND DIP RATE VARIABLES PRE TREATMENT

Desaturation dip rates are event rates which include some information about extent of desaturation and so good correlations with AHI would be expected for both TOI and SaO_2. There were good correlations between AHI and event related TOI and SaO_2 dip rates (c=0.79 - 0.91), slightly less good with mean min sat and mean sat dip (c = 0.54-0.70) (Table 53).

Table 53. Correlation coefficients for the relationship between poly variables and dip rate variables for SaO_2 and TOI from baseline pretreatment polysomnography (n=55)

SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, AHI = apnoea hypopnoea index, mean min SaO_2 = mean of minimum values during apnoeas, mean SaO_2 dip = mean of SaO_2 drops during apnoea.

	AHI	Mean min SaO_2	Mean SaO_2 dip
4% SaO_2 diprate	0.913**	-0.610**	0.702**
2% TOI dip rate	0.907**	-0.542**	0.631**
4% TOI dip rate	0.793**	-0.576**	0.660**

** $p<0.01$

Looking at REM event rates and arousal index, there was a strong relationship between REM dip rates for both TOI and SaO_2 and REM AHI (Table 54) as both are measuring the event rate during the same stage of sleep. The relationship between REM dip rates and arousal index was weaker than that with overall AHI.

Table 54. Correlation coefficients for relationship between AHI, AI and REM AHI and dip rate variables for SaO_2 and TOI from baseline pretreatment polysomnography (n=43)

SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, AHI = apnoea hypopnoea index, AI = arousal index, REM = rapid eye movement.

	AHI	AI	REM AHI
4% SaO_2 diprate	0.959**	0.565**	0.651**
4% SaO_2 dip rate (REM)	0.650**	0.257	0.896**
2% TOI dip rate	0.945**	0.600**	0.617**
4% TOI dip rate	0.873**	0.632**	0.536**
2% TOI dip rate (REM)	0.631**	0.310*	0.871**
4% TOI dip rate (REM)	0.700**	0.317*	0.888**

** $p<0.01$, * $p<0.05$

11.12 RELATIONSHIP BETWEEN DIP RATE AND AUC VARIABLES PRE TREATMENT

We were also interested in whether our two ways of summing TOI ranked the OSA severity of different subjects in the same order. The two methods differed both in what they measured (one an event rate, the other a measure of total desaturation) and in the output used to calculate them (one an analogue output to the polysomnography, the other a separate digital output).

Overall the two methods of quantifying TOI did not correlate well with each other (Table 55). "% obs 10% below maximum" correlated with 2% and 4% dip rates. The 4% dip rate correlated with some of the AUC measures. These intercorrelations may mean that the 4% TOI dip rate and the "% obs 10% below maximum" are the most useful outcomes to use in studies.

Table 55. Correlation coefficients for the relationship between TOI AUC variables and TOI dip rate variables from baseline pretreatment polysomnography (n=45)

AUC = area under the curve (variation below maximum), maximum defined as value of TOI that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are compared here with TOI dip rates. REM = rapid eye movement

	2% dip rate	4% dip rate	2% dip rate (REM)	4% dip rate (REM)
%observations 2% below maximum	0.158	0.173	-0.137	-0.063
%observations 4% below maximum	0.220	0.249	-0.102	-0.067
%observations 10% below maximum	0.356*	0.372*	0.016	0.055
AUC below maximum	0.300	0.340*	-0.006	0.022
AUC 2% below maximum	0.302	0.336*	-0.001	0.034
AUC 4% below maximum	0.296	0.333*	0.000	0.031
AUC 10% below maximum	0.199	0.241	0.005	0.028

** $p<0.01$ *$p<0.05$

There were better correlations between the 4% saturation dip rate and SaO_2 AUC variables (Table 56). However these correlations remain worse than those between the 4% dip rate

and AHI, suggesting that the 4% dip rate is closer to the event rate than to the most sensitive measure of summed desaturation.

Table 56. Correlation coefficients for the relationship between SaO_2 AUC variables and SaO_2 dip rate variables from baseline pretreatment polysomnography (n=45)

AUC = area under the curve (variation below maximum), maximum defined as value of SaO_2 that 99% of observations are below. % of observations, and AUC below three thresholds below maximum are compared here with SaO_2 dip rate variables. REM = rapid eye movement.

	4% dip rate	4% dip rate (REM)
%observations 2% below maximum	0.371*	0.232
%observations 4% below maximum	0.518**	0.314*
%observations 10% below maximum	0.729**	0.382*
AUC below maximum	0.716**	0.399**
AUC 2% below maximum	0.713**	0.387*
AUC 4% below maximum	0.707**	0.390*
AUC 10% below maximum	0.640**	0.340*

** $p<0.01$, * $p<0.05$

11.13 SUMMARY

11.13.1 It is possible to use NIR cerebral oxygenation monitoring in unmanned full night polysomnography.

We have shown that it is possible to record 8 hours of TOI data from an overnight unmanned sleep study, with only 3 sets of data discarded because of technical problems, all of whom refused a repeat study. No side effects from the probe were observed.

11.13.2 Summary measures from an overnight study can be calculated for TOI which differ from measures based on SaO2 and conventional polysomnography measures.

We have described results for two methods of summarizing TOI from overnight studies: AUC and dip rates. We have also calculated measures for SaO_2 using the same methods.

We have compared them both to conventional polysomnography measures of OSA severity. Our results suggest that in general the AUC measures for SaO_2 were more closely correlated to conventional polysomnography measures than those for TOI. The fact that these correlations exist suggests that the method used for calculating AUC (identical for SaO_2 and TOI) is not invalid, particularly as correlations with oxygen measures (mean min sat, mean sat dip) are closer than those with AHI. The TOI AUC measures can only be validated against clinical outcome.

Of the measures of percentage time below a particular saturation, the "% obs 10% below maximum SaO_2" seems to correlate best with conventional measures, which supports the use of the analogous T90 as a sleep study outcome.

AUC measures on CPAP will be affected by the fact that most fluctuation in saturation on CPAP will not be due to apnoea, and so will not correlate well with poly measures of OSA severity, however may be appropriate for use in outcome studies, depending on whether repetitive desaturation or summed desaturation has the greater effect on neuropsychological function.

The event rates AHI, 4% SaO_2 dips, 2% and 4% TOI dips, were all (in this study) calculated manually from the polysomnography trace, and unlike conventional algorithm derived dip rates, were apnoea associated. The values were therefore similar and correlated well with conventional measures.

These derived values of TOI and SaO_2, both AUC and dip rates, could now be used as single measures for each patient to be compared with neuropsychological function in a prospective study to see if cerebral oxygenation affects daytime neuropsychological function. We have described algorithms for their calculation, and given means and ranges in approximately 50 subjects with OSA, on and off CPAP. As is conventional (but maybe not meaningful) we have compared these new measures against the conventional measure of OSA severity AHI. If TOI does prove to be a predictor of neuropsychological outcome, we have shown that it is not well predicted by conventional saturation polysomnography variables.

12. NEUROPSYCHOLOGICAL FUNCTION IN RESPIRATORY FAILURE SECONDARY TO CHRONIC LUNG DISEASE

12.1 INTRODUCTION

So far this thesis has concentrated on obstructive sleep apnoea, where the baseline saturation is normal but subjects experience repetitive significant desaturations of short duration during the night. Nocturnal desaturation and sleep disruption affect daytime function, and it is possible that direct measurement of cerebral saturation with near infra-red spectroscopy may predict daytime neuropsychological function better than conventional sleep studies. The other group of patients in whom desaturation affects neuropsychological function is those with respiratory failure. Here the hypoxaemia is chronic and various compensatory mechanisms exist. Again it is possible that treatment benefit may be predicted by cerebral oxygenation changes so this is a patient group where near infrared spectroscopy may be useful.

Chronic obstructive pulmonary disease is characterized by airflow obstruction, which is usually progressive, not fully reversible and does not change markedly over several months (156). In severe disease hypoxia may result mainly because of ventilation perfusion mismatch, although hypoventilation and diffusion impairment may also contribute (157). In the long term respiratory failure defined by arterial hypoxaemia leads to pulmonary hypertension, peripheral oedema and cor pulmonale. The brain is very sensitive to hypoxia, but chronic low levels of SaO_2 are tolerated better than acute changes, probably due to adaptive mechanisms. Hence respiratory failure provides a second model in which to study the effects of cerebral oxygenation on neuropsychological function. This chapter

reviews studies in patients with COPD looking at neuropsychological function, the effects of supplementary oxygen and cerebral haemodynamics. These studies are not extensive and are variable in design, so that conclusions drawn are tentative.

12.2 OXYGEN TRIALS

It was not possible to give long term oxygen at home until a practical portable oxygen source was developed in the late 1960s. The early trials of supplementary oxygen in COPD used neuropsychological function as an outcome measure. A study carried out in 1974 of constant administration of oxygen at 2l/min to 12 subjects with severe COPD and hypoxaemia, demonstrated improvement in exercise tolerance, neuropsychologic functioning and ability to carry out activities of daily living despite no change in lung function. Highly significant improvement was seen in 9 out of 10 of an array of tests designed to assess neuropsychological function (158). Benefits occurred despite partial reversal of compensatory mechanisms, ie decreases in hematocrit, haemoglobin, and red cell 2,3 DPG. As a result of this and other small studies showing clinical benefit, large controlled studies of long term oxygen administration were set up in the USA (Nocturnal Oxygen Therapy Trial; NOTT) (159) and the UK (MRC) (160). In the NOTT study 203 patients with hypoxemic COPD (PaO2 < 55mmHg, or <59mmHg with evidence of cor pulmonale) were randomly allocated to either continuous oxygen therapy or 12 hour nocturnal oxygen therapy and followed for at least a year. The overall mortality in the nocturnal group was 1.94 times that of the continuous group (159). The MRC recruited 87 subjects who all had COPD, severe hypoxaemia (PaO2 between 40 and 60mmHg), carbon dioxide retention and a history of oedema, and gave them oxygen at 2l/min for at least 15hours a day. 19 out of 42 oxygen treated subjects died in 5 years of follow up compared to 30 out of 45 controls (160). Long term oxygen prescription for COPD in the UK is based on the result of these two trials. The level of hypoxaemia selected for entry into these trials is related to definitions of respiratory failure based on the shape of the oxygen dissociation curve. The sigmoid shape of the curve means that arterial saturation is maintained above 90% until PaO2 falls to about 50mmHg, after which the curve is more steep and saturation falls off rapidly. A further trial performed in Poland by Gorecka et al showed no increase in survival at 3 years in 135 patients with moderate hypoxaemia (56-65mmHg) randomized to LTOT or control and provides the evidence to restrict oxygen prescription to patients with severe hypoxaemia (161). As well as improving survival,

LTOT has other benefits including slowing of deterioration of pulmonary haemodynamics, reduction of secondary polycythaemia, improved sleep quality, increase in renal blood flow, reduction in cardiac arrhythmias and neuropsychological benefit (162). In the NOTT trial, moderate to severe impairment on neuropsychological testing suggestive of cerebral dysfunction was found in 42% of patients compared to 14% of controls prior to oxygen therapy (163). Subgroup analysis of the trial results showed survival benefit was particularly marked in patients with more severe brain dysfunction and mood disturbance (159).

It is possible that direct measurement of cerebral oxygenation and changes in relation to oxygen therapy may be more helpful in predicting neuropsychological benefit than arterial saturation measurements. If neuropsychological dysfunction correlates with cerebral oxygenation, it may be possible to identify a group of patients who will particularly benefit from oxygen therapy. Adaptation to hypoxia through polycythaemia, 2,3 DPG and cerebral blood flow alterations may maintain cerebral oxygenation, despite peripheral hypoxaemia, and these adaptive mechanisms may vary between patients.

12.3 NEUROPSYCHOLOGICAL FUNCTION IN COPD

The mechanism for cognitive impairment in hypoxaemic COPD is not known and is probably multifactorial. Lack of oxygen may be a possible cause. The proportion of subjects with neuropsychological deficit rose from 27% in mild hypoxaemia to 61% in severe hypoxaemia in about 300 patients from the combined NOTT and Intermittent Positive Pressure Breathing (IPPB) trials (164). This dose response relationship observed between hypoxaemia and neuropsychological deficit supports an aetiological role for hypoxaemia, particularly as neither pulmonary function tests nor arterial pCO_2 were significantly correlated with neuropsychological test scores. There was also no correlation with exercise capacity or mood state, suggesting that the correlation with hypoxia is not just a non-specific effect of more severe illness. A study of cognitive function in subjects with mild to moderate COPD without hypoxia using mini-mental state examination suggested no difference to controls (165) which suggests that COPD without respiratory failure has no effect on cognitive function, although the mini-mental state exam is not very sensitive.

It has been suggested that neuropsychological deficit in hypoxic COPD may follow a specific pattern. Incalzi et al (166) found that 48.5% of 36 patients with COPD had a specific pattern of cognitive impairment characterised by a dramatic impairment in verbal and verbal memory tasks with well-preserved visual attention. This pattern differed from Alzheimer type dementia controls and multi infarct dementia controls. Cognitive impairment correlated with age and with duration of hypoxic and hypercapnoeic respiratory failure. A more recent study from the same group using mapping of brain perfusion with single photon emission computed tomography as well as cognitive testing suggested that COPD subjects performed better than Alzheimer subjects and worse than controls and that performance correlated with anterior cerebral hypoperfusion (167). Reversibility of cognitive deficit with LTOT is probably partial. Patients studied in one study cited above (166) had been receiving oxygen therapy "from the start of oxyhaemoglobin desaturation" and still had neuropsychological deficit correlating with the duration of respiratory failure. This suggests that the cognitive deficit is not preventable by current treatment. However in the NOTT trial all measures of neuropsychological function improved significantly after 12 mths of oxygen treatment (159), which suggests that established deficit can be reversed in part.

If LTOT can partially reverse neuropsychological deficit, another question arises as to whether there is an acute effect of oxygen on neuropsychological function (ie does it make a difference if the testing is carried out on oxygen or not). Cohen et al (168) found no effect on neuropsychological function (memory, learning, sustained concentration and motor and visuomotor speed) of discontinuing LTOT treatment for 4 hours in 12 patients, serving as their own controls. Heaton et al (169) reporting results of neuropsychological follow up in the NOTT trial note that the improvements they observed were not as large as in 2 previous small studies where neuropsychological tests were carried out pre treatment off oxygen and post treatment on oxygen. The NOTT protocol carried out both tests off oxygen, and they suggested in the light of their results that there may be two mechanisms underlying the effect of oxygen on brain function. When oxygen was administered to normal volunteers in a double blind study, it enhanced cognitive performance compared to participants who inhaled air (170). Scalvini et al (171) found that autonomic nervous system function was deranged in 11 patients with chronic hypercapnoeic respiratory failure and that the abnormalities were partially reversed by oxygen administration.

Therefore any mechanism for neuropsychological dysfunction in hypoxic COPD seems to involve hypoxia, and be partially reversed by both chronic and possibly acute oxygen administration.

12.4 MECHANISMS OF NEUROPSYCHOLOGICAL DYSFUNCTION

As previously discussed for OSA it is not clear whether the general mechanism by which hypoxia causes neuropsychological dysfunction is direct ischaemia or effects on enzyme metabolism. Alterations in cerebral metabolism in COPD have been demonstrated using proton magnetic resonance spectroscopy, however correlation between this and neuropsychological testing was poor (172).

12.5 CEREBRAL HAEMODYNAMICS IN RESPIRATORY FAILURE

If we propose to measure cerebral oxygenation in COPD, we are interested in determinants of cerebral blood flow as well as arterial saturation, as cerebral oxygen supply depends on both these factors. Focal changes in cerebral perfusion in hypoxic subjects with COPD have been described above (167). One of the main features of respiratory failure in COPD is hypercapnoea (Type 2 respiratory failure) which is due to a combination of VQ mismatch and inadequate ventilation. Daytime hypercapnoea is rarely seen in OSA unless there is associated gross obesity or parenchymal lung disease. Hypercapnoea is one of the main stimulants to cerebral blood flow, and so may account for changes in cerebral oxygen supply. Although the increased CBF in hypercapnic respiratory failure could be seen as an adaptive mechanism, it may be responsible for raised intracranial pressure with accompanying papilloedema and headaches if acute. There is some interest in the measurement of cerebrovascular reactivity in these subjects to see if they retain the usual cerebral blood flow response to changes in pH or pCO_2 despite resting hypercapnia. This has been investigated by measuring response to acute changes in carbon dioxide tension in 17 chronic hypercapnic COPD patients, 16 normocapnic COPD patients and 15 healthy subjects using NIRS cerebral blood volume measurements (173). This study showed that the slope of the cerebrovascular response to CO_2 was significantly lower in both COPD groups than in normals, but did not differ between the groups. They also showed absolute cerebral blood volume measurements to be reduced in both COPD groups compared to

controls, and to be significantly lower in normocapnic compared to hypercapnic subjects. The reduction in cerebral blood volume measured in the frontal region (because of NIRS probe positioning limitations), is consistent with the findings of anterior cerebral hypoperfusion by Incalzi's group. This would therefore fit with either regional hypoperfusion or a general effect. Another study by van de Ven et al showed that induction of chronic metabolic acidosis and alkalosis had no effect on cerebrovascular reactivity in16 normocapnic and 17 hypercapnic COPD patients also using NIRS CBV measurements (174).

Cerebral oxygenation has been measured during exercise in subjects with respiratory failure using NIRS and simultaneous MCA Doppler (175). During exercise breathing air, cerebral blood flow and deoxygenated haemoglobin increased, oxyhaemoglobin was unchanged and SaO_2 decreased. During exercise with supplementary oxygen, the CBFV increased by a similar amount to that on air, but O2Hb also increased while HHb decreased, ie the exercise induced increase in cerebral perfusion was not affected by hyperoxia.

Arterial saturation in COPD is known to worsen at night. Cerebral saturation has been measured at night using bilateral frontal NIRS probes in 6 subjects with severe COPD without OSA who did not fit the criteria for LTOT, and compared with SaO_2. Falls in SaO_2 were accompanied by bilateral falls in cerebral tissue saturation, which in one case were asymmetrical, with possible evidence of a steal phenomenon (176). The clinical relevance of this finding is currently unclear.

12.6 EFFECT OF SMOKING ON CEREBRAL BLOOD FLOW

Almost all patients with COPD have smoked at some stage and many continue to smoke. Many patients in the MRC LTOT (160) and NOTT (177) trials were current smokers, as smoking was not an exclusion criteria (178). Cigarette smoking has complex effects on cerebral vessel function, which appear to be different acutely and chronically, but interpretation of the studies is complicated by the fact that a radio-isotope based technique is used to measure CBF in chronic studies and Doppler CBFV in acute studies. Regional cerebral blood flow by 133-xenon inhalation is reduced in smokers in several studies (179-181). Regional CBF also goes down with age (179, 181) and one study showed a significant reduction in regional CBF only in elderly smokers (182). The rCBF in subjects who quit smoking is between that of current smokers and never smokers (183) and there is

longitudinal evidence that perfusion improves after 1year (183) and 9 years (184) in small numbers of subjects. Long term effects of smoking on cerebral perfusion may be due to accelerated atherosclerosis and increased viscosity.

Measurements of CBFV on "volunteers" while smoking cigarettes show an increase in Doppler CBFV (185-190). Whether this is due to a true increase in CBF or whether it is due to cerebral vasoconstriction is unclear. Smoking increases arterial blood pressure (186, 190) and this increased pressure may be associated with increased CBF. However nicotine injection in mice reduces cerebral blood flow measured with radionuclides (191) and simultaneous measurement of Doppler CBFV and isotope regional CBF in 6 smokers showed an increase in the former with a significant fall in the latter (186). Nicotine in cigarettes therefore probably causes generalised vasoconstriction including cerebral vessels, and the chronic effect of this is to accelerate atherosclerosis.

12.7 SUMMARY OF PREVIOUS NIRS STUDIES IN COPD

In summary there have been several studies in hypoxic COPD using NIRS. Unlike OSA, there are no frequent fluctuations in cerebral oxygenation occurring spontaneously, so these studies have observed cerebral haemodynamic responses in these patients in response to stimuli such as hypercapnoea, exercise and sleep. However the effect of supplementary oxygen on cerebral oxygenation has not been well described, and specifically whether subjects vary in their responses to oxygen or whether cerebral saturation response can be predicted from peripheral pulse oximetry. This issue was addressed in the validation studies described in the next chapter, to explore the potential of NIRS as part of the work up for LTOT.

13. USE OF NEAR INFRA-RED SPECTROSCOPY IN SUBJECTS WITH CHRONIC HYPOXIA

13.1 OVERALL HYPOTHESIS

13.1.1 Measurement of cerebral oxygenation using near-infra red spectroscopy gives additional valid information when compared to measurement of arterial oxygen saturation alone

13.2 HYPOTHESES UNDERLYING ANALYSIS IN THIS CHAPTER

13.2.1 Characteristics of TOI differ from characteristics of arterial oxygen saturation.

13.2.2 TOI changes during oxygen challenge cannot be predicted from arterial oxygen saturation alone.

13.2.3 Cerebral blood volume can be measured in subjects with COPD using oxygen challenge

13.3 INTRODUCTION

We have seen that patients with chronic hypoxia in association with chronic lung disease differ from those with OSA in that they do not undergo frequent spontaneous changes in saturation and cerebral blood flow. In order to investigate the relationship of TOI to saturation in this group, a stimulus needs to be applied and the response to it recorded. Other previous studies using NIRS in COPD have used stimuli such as hypercapnia, exercise or sleep. We chose to use supplementary oxygen and measure resulting changes in NIRS parameters. This would provide information about the acute effects of oxygen on cerebral oxygenation. This is of interest because of evidence that hypoxia does affect neuropsychological function and that this effect is partially reversible with LTOT. There is a possibility that the cerebral oxygenation response to supplementary oxygen might predict neuropsychological improvement on LTOT. First we needed to document TOI changes in response to oxygen in subjects who are chronically hypoxic, to show that they could not be predicted by SaO_2 alone and that they differed between people. No work was done using neuropsychological testing in this patient group as part of this thesis.
This chapter describes the changes in NIRS parameters observed during oxygen challenge in hypoxic patients with COPD. Absolute cerebral blood volume was calculated from oxygen challenge data. Cerebral oxygenation depends on arterial saturation and cerebral blood flow. We had no measurements of cerebral blood flow except for changes in total haemoglobin (relative blood volume) so relationships between cerebral oxygenation (TOI), SaO_2 and total haemoglobin during oxygen challenge were examined.

13.4 METHODS

This study was performed by myself and Dr Arschang Valipour, Research Associate from Vienna, Austria, under the supervision of Professor S Spiro and Dr H Makker, Department of Thoracic Medicine, University College London Hospitals, between June 1999 and May 2000.

13.4.1 Subject recruitment

A pilot study was carried out on 8 subjects to establish the protocol. These patients consisted of 4 patients with COPD, 2 with bronchiectasis and 2 with nocturnal hypoxaemia.
CBV measurements were then carried out more formally on 11 subjects, all with COPD, and all with an oxygen concentrator or being assessed for provision of home oxygen (oxygen saturation <92%). Subjects were recruited from the wards and from out patient clinics after giving details of the study to doctors and respiratory nurses in these clinics.

Ethics approval was granted from the UCLH ethics committee and full written consent was obtained from each subject. People undergoing oxygen assessment had arterial blood gas tensions measured on the day of the study, otherwise the most recent ABG measurement in the notes was recorded. We did not have ethical approval to take ABG specimens that were not clinically indicated.
When considering cerebral haemodynamics in COPD smoking history needs to be taken into account. The policy of the Middlesex Hospital at this time was to assess patients for LTOT only if they had given up smoking, so all patients recruited denied current smoking. Objective measurements of current smoking eg urinary cotinine measurements were not made and it is known that a percentage of people who deny current smoking to a doctor, are continued smokers, and up to 20% of patients on LTOT continue to smoke (192). However no patients had smoked within 2 hours of the oxygen challenge test and so no acute or dynamic effects of cigarette smoking on cerebral haemodynamics would have been observed.

13.4.2 Protocol

Subjects undertook the study lying semirecumbent on a bed in a quiet hospital sideroom. All subjects were breathing room air (off supplementary oxygen for at least 30mins) at the start of the study.
Cerebral oxygenation was monitored using the NIRO300. Optodes were applied to the left forehead with a self adhesive pad as described previously. A pulse oximeter probe was

attached to the left index finger (Pulseox 7 Minolta, now Anandic Medical Systems, Diessenhofen, Switzerland). A venturi mask was positioned loosely around the patient's neck, but not connected to oxygen. This was because it was important not to move the NIRO probe after recording was started, and in this position the mask could be lifted into place without touching the NIRO probe. Recording was then commenced. We did not at this time have a working analogue to digital converter enabling simultaneous oximetry and NIRO recording, so recordings of oxygen saturation, TOI, OHb, HHb, cytox were manually taken from the pulse oximeter and NIRO display every 20-30 seconds. In addition the raw data of TOI, OHb, HHb and cytox were downloaded into a computer file every 5s. The pulse oximeter averaging time is 5s. After about 5 minutes of baseline recording the oxygen mask was put into position and oxygen was switched on at a flow rate of 2l/min to give 24% oxygen. Recordings were continued for 5minutes or until the TOI and oxygen saturation readings had been stable for 3 successive recordings. The venturi attachment was then changed to 35% and the oxygen flow rate increased accordingly. Recordings were again continued for 5minutes or until the TOI and oxygen saturation readings had been stable for 3 successive recordings. The oxygen was then switched off and the mask removed from the face. Recordings were continued until oxygen saturation had returned to within 2% of baseline.

13.5 ANALYSIS

Changes in TOI, oxygen saturation, and total haemoglobin were observed during oxygen challenge. Relationships between these parameters were examined in each subject and in the whole patient group correcting for interpatient differences. Ratio of total SaO_2 to total TOI change was calculated for each patient. Total change in cytochrome oxidase during oxygen challenge was also measured.

Absolute CBV is one of the few absolute measurements that can be derived from standard NIRS measurements Ohb and HHb. As an absolute measure it should be comparable between subjects and between studies. It can be derived from response to oxygen challenge in normal adults, provided a graph of difference between oxygenated and deoxygenated haemoglobin against oxygen saturation is a straight line. This assumes there is no change in CBF or oxygen consumption in response to increased FiO_2. In order to achieve the necessary change in SaO_2 in normal adults, the inspired oxygen is transiently

reduced. In COPD patients who are hypoxic the necessary 6% change in saturation can be brought about by increasing FiO_2.

Calculation of CBV was performed using the equation:

$$CBV = \frac{64{,}500 \times 100}{1{,}000{,}000 \times 1.05 \times 10 \times 2 \times 0.69} \times \text{gradient} \times \frac{100}{(Hb)}$$

where 1.05 is cerebral tissue density, 0.69 is cerebral large to small vessel haematocrit ratio, 64,500 is the molecular weight of haemoglobin and gradient is the gradient of a graph of Hbdiff in μM against oxygen saturation in fractional change (93). Graphs were plotted of Hbdiff against oxygen saturation from the start of recording until the oxygen was switched off.
Gradients were considered acceptable if correlation coefficients were >0.5.
DPF (differential pathlength factor) was assumed as 6.26(96).

13.5.1 Statistics

Relationships between parameters during oxygen challenge were examined using scatter plots and then simple regression analysis. $P<0.05$ was taken to be significant. Results from different subjects were combined in a two level regression as described previously.

13.6 RESULTS

13.6.1 Preliminary pilot study

This established that there were changes in cerebral oxygenation occurring in response to oxygen challenge in all patients, ie that cerebral oxygenation is not maintained by autoregulation of blood flow in the short term. One of the patients with severe bronchiectasis had a baseline oxygen saturation below 60% (and attended as an outpatient, see photocopied oxygen saturation trace Fig 50) - his response to oxygen challenge is illustrated in this figure and below (Fig 51). Supplementary oxygen was delivered between timepoint A and B. This resulted in a rise in SaO_2, TOI and Ohb and a fall in HHb. Note that the cytochrome oxidase trace showed a minimal decrease during the oxygen administration which did not suggest that his respiratory chain was limited by oxygen

availability even at these low saturations. A rise in total haemoglobin is noted when the oxygen is switched off; this is presumably a blood flow response to hypoxia. A rise in pulse rate is noted on the oximetry trace at the same time.

Figure 50. Saturation trace during oxygen challenge for subject with severe bronchiectasis and hypoxaemia described in text

Photocopied pulse oximeter trace with SaO_2 scale on y axis from 50% to 100% and clock time on x axis. Initially lower trace is SaO_2 and higher trace is pulse. Oxygen challenge between A and B.

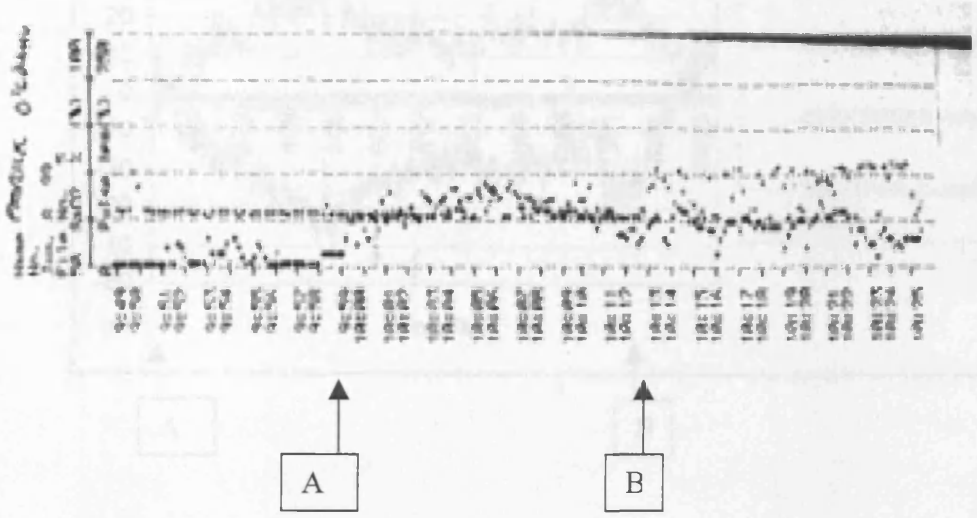
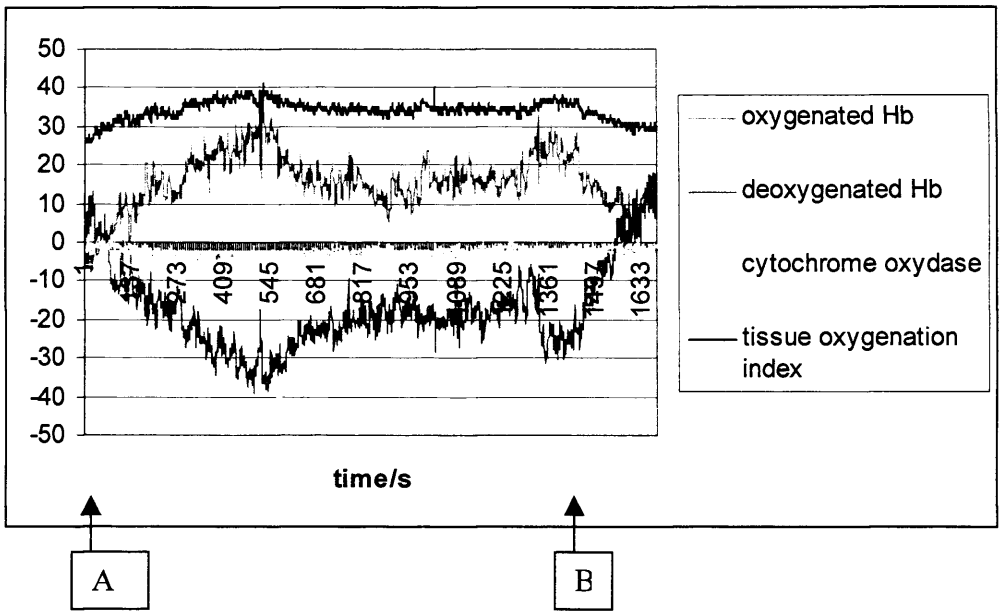


Figure 51. Changes in NIRS parameters during oxygen challenge in subject with severe bronchiectasis
Units on y axis are μM from an arbitrary baseline for Hb and cytochrome oxidase, and % for tissue oxygenation index. Oxygen challenge applied between A and B.



13.6.2 CBV pilot study

Subjects

Subjects included 5 men and 6 women, all with COPD. Their mean age was 69.4 +/- 7.1 years.

6 were outpatients, 5 were inpatients; all were stable and not during acute exacerbation.

Six were already receiving long term oxygen therapy (LTOT), 5 were being assessed for LTOT.

Characteristics of the subjects are given in Table 57.

Table 57. Spirometry and othe characteristics of COPD patients

IP= inpatient, OP = outpatient, FEV1 = forced expiratory volume in the first second, FVC = forced vital capacity, LTOT = long term oxygen therapy

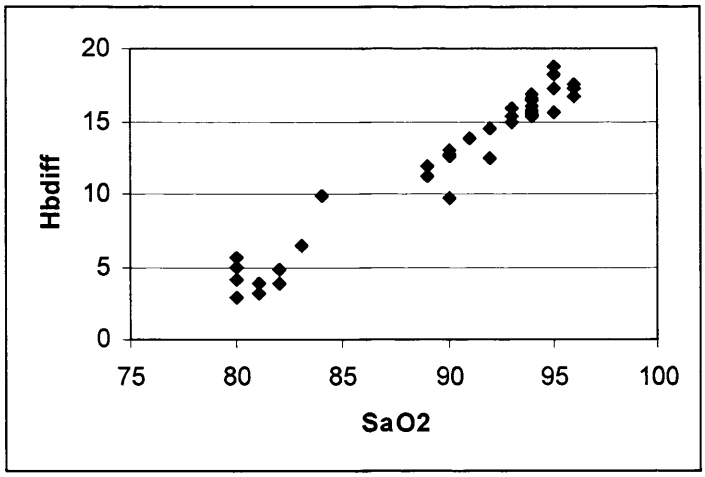
ID	*Age /yr*	*diagnosis*	*Arterial pO_2 /kPa*	*Arterial pCO_2 CO_2/kPa*	*IP/OP*	*FEV1 /l*	*FVC /l*	*On LTOT*
hi	73/m	COPD	9.6 (31)	7.7	op	0.83	2.12	Y
ja	79/f	COPD	8.48	8.06	ip			Y
la	57/f	COPD	7.52	5.17	op	0.7	1.05	N
le	71/m	COPD	7.2	5.99	ip	1.09	2.51	Y
ma	63/f	COPD	9.59	4.62	ip	0.91	2.12	N
mo	68/m	COPD	6.91	6.47	op			N
re	60/f	COPD	7.38	4.87	ip	0.84	1.79	N
ro	70/m	COPD			op	0.52	1.47	Y
st	75/m	COPD, CCF			op	0.9	2.01	Y
cz	78/f	COPD	12.2(35%)	6.99	ip	0.80	1.63	Y
we	69/f	COPD	7.01	8.07	op	0.82	1.61	N

CBV calculations

In 11 patients a plot of Hbdiff against oxygen saturation regressed significantly to a straight line (eg Fig 52).

Figure 52. Hbdiff (μM) against SaO_2 (%) in pilot study subject (HI)

Hbdiff = deoxygenated haemoglobin subtracted from oxygenated haemoglobin in μM. SaO_2 = arterial oxygen saturation in %.



Calculated CBV values appear to be in the correct range (Table 58) with a mean value of 2.52 +/- 0.69 ml/100g. Previous studies have quoted baseline CBV measurements of 1.1-8.6 ml/100g. There is no relationship between CBV and a single pCO_2 measurement, however not all pCO_2 measurements were contemporaneous.

Table 58. CBV calculations in COPD patients

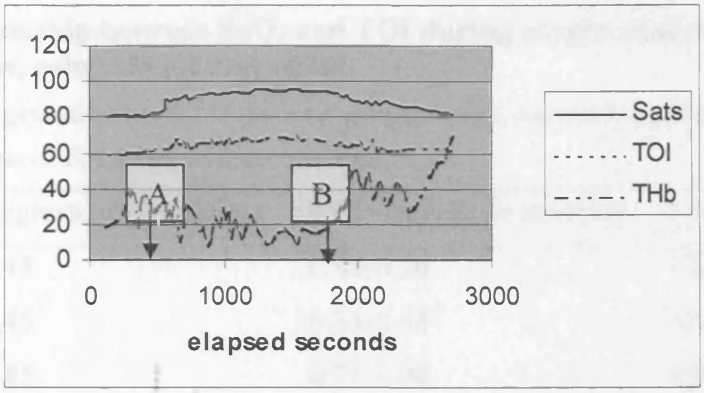
CBV is calculated from the formula quoted above (93). Gradient is the gradient of a graph of HbDiff in μM against SaO_2 in fractional change, the R2 and p values are from this regression graph. HbDiff is the difference between oxygenated and deoxygenated haemoglobin. CBV = calculated cerebral blood volume. pCO_2 = arterial partial pressure of carbon dioxide.

Patient	Gradient	R^2	p	Hb	CBV ml/100g	recent pCO_2 kPa
HI	0.911	0.96	<0.05	14.1	2.88	7.68
CZ	0.979	0.89	<0.05	14.0	3.11	6.99
MA	1.04	0.64	<0.05	12.7	3.65	4.62
LE	0.669	0.58	<0.05	13.1	2.27	5.99
MO	0.522	0.60	<0.05	15.4	1.51	6.47
ST	1.174	0.70	<0.05	15.6	3.34	-
LA	0.861	0.76	<0.05	14.4	2.66	5.17
RE	0.792	0.75	<0.05	14.3	2.47	4.87
WE	0.676	0.87	<0.05	13.1	2.30	8.07
RO	0.584	0.64	<0.05	13.3	1.95	-
JA	0.517	0.90	<0.05	14.6	1.58	8.06

TOI changes in relation to saturation changes during oxygen challenge

Baseline oxygen saturations were 80 - 94%, and baseline TOI readings were 53 - 67%. There was no correlation between baseline TOI and saturation. During oxygen challenge both TOI and SaO_2 increased in all patients and then returned to near baseline following removal of supplementary oxygen (Eg Figure 53, supplementary oxygen applied between A and B). For the purposes of the following analyses only the sections of data during oxygen administration were used, and the sections during the recovery period were not included.

Figure 53. Changes in TOI, SaO_2 and total haemoglobin during oxygen challenge (HI).
Sats = SaO_2 = arterial oxygen saturation in %, TOI = tissue oxygenation index in %, THb = total haemoglobin in arbitrary units.



Maximum and minimum TOI and SaO_2 during oxygen challenge are shown in Table 59. Patients differed in the ratio of SaO_2 change to TOI change. This ratio tended to increase with decreasing baseline SaO_2 but this was not significant.

Table 59. SaO_2 and TOI measurements during oxygen challenge
SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, values are absolute minima and maxima during oxygen challenge.

Patient	baseline SaO_2 %	max SaO_2 %	baseline TOI %	max TOI %	Ratio of SaO_2 to TOI change
HI	80	96	60	68	2
CZ	91	97	67	72	1.2
MA	88	94	63	71	0.75
LE	93	98	66	72	0.83
MO	84	95	56	63	1.57
ST	94	98	60	70	0.4
LA	86	95	55	66	0.82
RE	89	97	61	64	2.67
WE	88	96	61	69	1.0
RO	88	98	54	62	1.25
JA	82	93	53	60	1.57

There was a significant correlation between SaO_2 and TOI during the oxygen challenge in all patients (27-45 readings per subject) with regression coefficient varying from 0.29 to 1.30 (Table 60).

Table 60. Relationship between SaO_2 and TOI during oxygen challenge in each subject, using simple regression.

SaO_2 = arterial oxygen saturation, TOI = tissue oxygenation index, regression is of SaO_2 against corresponding values of TOI during oxygen challenge.

Subject ID	Regression coefficient	95% confidence intervals	p value	R^2
1	0.44	0.38-0.50	<0.001	0.86
2	0.45	0.35-0.54	<0.001	0.71
3	0.85	0.71-1.00	<0.001	0.76
4	0.48	0.26-0.70	<0.001	0.38
5	0.69	0.29-1.10	0.002	0.33
6	0.48	0.38-0.58	<0.001	0.71
7	0.29	0.22-0.37	<0.001	0.60
8	0.63	0.45-0.81	<0.001	0.60
9	1.30	0.92-1.69	<0.001	0.58
10	0.66	0.52-0.81	<0.001	0.72
11	0.68	0.59-0.78	<0.001	0.87

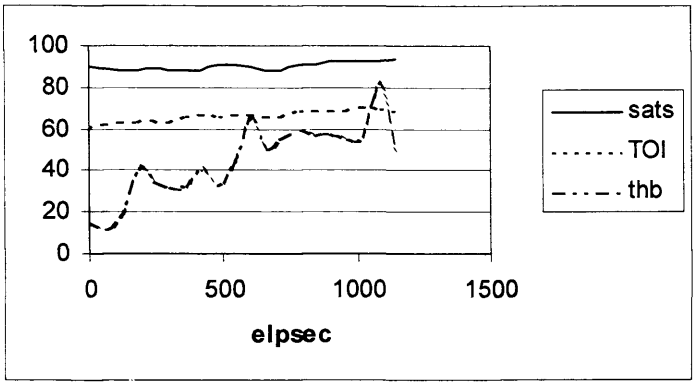
Changes in total haemoglobin (relative blood volume) during oxygen challenge

In 6 subjects total haemoglobin (THb) fell during the oxygen challenge, eg Figure 53.

In 2 subjects total haemoglobin increased during the oxygen challenge, eg Figure 54.

Figure 54. Example of rise in THb during oxygen challenge (MA)

Sats = SaO_2 = arterial oxygen saturation in %, TOI = tissue oxygenation index in %, THb = total haemoglobin in arbitrary units, elpsec = elapsed seconds.



SaO_2 values were correlated with the corresponding total haemoglobin values (relative blood volume) during the oxygen challenge for each subject (Table 61). The regression coefficient shows how the two parameters are related and is positive if both increase during oxygen challenge and negative if there is a fall in relative THb.

Table 61. Relationship between SaO_2 and THb for each subject, using simple regression.

SaO_2 = arterial oxygen saturation, THb = total haemoglobin = sum of oxygenated and deoxygenated haemoglobin, regression is of SaO_2 against corresponding values of THb during oxygen challenge. Coeff is regression coefficient or the gradient of the regression line and is positive for a positive correlation and negative for an inverse correlation

Id	coeff	R^2	p
HI	-4.21	0.397	0.000
JA	-4.51	0.459	0.000
LA	-0.259	0.033	0.232
LE	-0.273	0.040	0.259
MA	0.638	0.286	0.015
MO	-2.09	0.343	0.000
RE	-1.09	0.388	0.000
RO	1.489	0.514	0.000
ST	0.199	0.020	0.413
SZ	0.378	0.011	0.548
WE	-0.134	0.001	0.858

Tissue carbon dioxide is known to be a determinant of cerebral blood flow. We therefore examined the relationship between the regression coefficients describing the change in CBV during oxygen administration and baseline pCO_2 recording. There were 5 subjects in whom the regression was significant and pCO_2 was available (Table 62).

Table 62. Regression coefficients for relationship between THb change and SaO_2 change, and baseline pCO_2

SaO_2 = arterial oxygen saturation, THb = total haemoglobin = sum of oxygenated and deoxygenated haemoglobin, pCO_2 = arterial partial pressure of carbon dioxide. The regression coefficient is the gradient of the regression line for SaO_2 against corresponding values of THb during oxygen challenge.and is positive for a positive correlation and negative for an inverse correlation.

id	Regression coefficient	pCO_2 /kPa
HI	-4.21	7.68
JA	-4.51	8.06
MA	0.638	4.62
MO	-2.09	6.47
RE	-1.09	4.87

A graph plotted of these regression coefficients against pCO_2 showed a significant relationship despite so few subjects (Figure 55). The correlation coefficient is –0.97.

Figure 55. Relation between change in THb during oxygen challenge and baseline pCO_2

THb = total haemoglobin = sum of oxygenated and deoxygenated haemoglobin, pCO_2 = arterial partial pressure of carbon dioxide. The regression coefficient is the gradient of the regression line for SaO_2 against corresponding values of THb during oxygen challenge.and is positive for a positive correlation and negative for an inverse correlation.

Changes in cytochrome oxidase during oxygen challenge

The following table (Table 63) shows the observed total changes in cytochrome oxidase during oxygen challenge, as well as the standard deviations of the cytox measurements. As the cytochrome trace starts from an arbitrary baseline, the standard deviation gives a further indicator of the variation in the cytochrome trace in addition to that given by the absolute change.

Table 63. Cytochrome changes during oxygen challenge

Δ SaO_2 is the total change in arterial saturation during the oxygen challenge, Δcytox is the total change in cytochrome oxidase, SD cytox is the standard deviation of the cytox trace during oxygen challenge.

id	Δ SaO_2 (%)	Δcytox (arbitrary units)	SDcytox
HI	16	+0.2	0.058
JA	11	+0.2	0.043
LA	9	+0.9	0.247
LE	5	-0.5	0.148
MA	6	-1.3	0.453
MO	11	+0.3	0.071
RE	8	-0.2	0.061
RO	10	-0.3	0.089
ST	4	+0.9	0.258
SZ	6	-1.1	0.238
WE	10	-0.2	0.048

The total change in cytox (Δcytox) was related to Δ SaO_2 as shown in the following table (Table 64).

Table 64. Relation between cytochrome and SaO_2 changes

Δ SaO_2 is the total change in arterial saturation during the oxygen challenge, Δcytox is the total change in cytochrome oxidase, SD cytox is the standard deviation of the cytox trace during oxygen challenge. Coeff is regression coefficient for simple linear regression in 11 subjects.

Independent variable	Dependent variable	coeff	R2	p
Δ SaO_2	Δcytox	-0.079	0.427	0.029
Δ SaO_2	SDcytox	-0.023	0.388	0.041

Pooled data

The effect of changes in CBV and SaO_2 on TOI in the pooled data was looked at in a two level regression, to correct for interindividual variation using the xtgee command of stata6 (146). During the oxygen challenge increasing oxygen saturation was associated with decreasing relative blood volume (regression coefficient -0.067, 95% CI -0.103 to -0.031, $p<0.001$). TOI values were significantly associated both with oxygen saturation (regression coefficient 0.56, 95% CI 0.52 -0.60, $p<0.001$) and relative blood volume (regression coefficient 0.33, 95%CI 0.23 - 0.44, $p<0.001$) in a multiple regression corrected for interpatient differences.

13.7 CONCLUSIONS

13.7.1 Characteristics of TOI differ from characteristics of arterial oxygen saturation.

We again observed variation in baseline TOI (53 – 67, median 60), but in this group there was also variation in baseline SaO_2 (80-94, median 88). The mean baseline TOI was 59.6, compared to 66.5 in the OSA subjects. There was no correlation between baseline TOI and saturation.

13.7.2 TOI changes during oxygen challenge cannot be predicted from arterial oxygen saturation alone.

We demonstrated that cerebral tissue saturation increased during challenge with 24% and 35% oxygen in subjects hypoxic from COPD. Although chronically hypoxic patients do have some compensatory mechanisms, cerebral blood flow changes clearly do not maintain constant cerebral oxygenation.

There was a significant relationship between SaO_2 and cerebral tissue saturation during oxygen challenge in all subjects, however the regression coefficient differed among subjects. This confirmed that TOI did not depend on SaO_2 alone in this patient group, and therefore suggested that another factor involved in cerebral oxygenation (blood flow or oxygen consumption) also alters during oxygen challenge.

Total haemoglobin (relative cerebral blood volume) does not remain constant during oxygen challenge. It increases in some subjects and decreases in others. Variations in CBV may be due to hypercapnoea and cerebrovascular reactivity. There was some suggestion that the change in CBV may be related to baseline pCO_2. The change in CBV per change in sat was related to pCO_2 as follows: patients with high CO_2 tended to have a fall in CBV on oxygen administration and patients with a low CO_2 tended to have a rise. The precise reason for this is not clear, particularly as we did not monitor pCO_2 continuously. It is possible that subjects with chronic hypercapnoea have cerebral vasodilatation and then vasoconstrict as a response to oxygen administration. Subjects with normal CO_2 may not show this response.

In multiple regression the TOI during oxygen challenge was shown to depend not only on SaO_2 but also on CBV. This provides additional (weak) evidence to validate TOI as a measure of cerebral oxygenation. The evidence is weak because it assumes that CBV changes measured using NIR can be used as a proxy for CBF changes and are not subject to extracranial contamination.

An important conclusion follows these findings. We have shown that cerebral blood volume does not remain constant during supplementary oxygen administration in chronically hypoxic patients. We have also shown that both CBV and SaO_2 affect cerebral oxygenation. It follows that the effect of supplementary oxygen on cerebral oxygenation will be modified by changes in CBV occurring during oxygen administration. This conclusion suggests that the effect of LTOT on cerebral oxygenation will be modified by cerebral blood flow changes and will not be predictable from the saturation response alone.

13.7.3 Cerebral blood volume can be measured in subjects with COPD using oxygen challenge

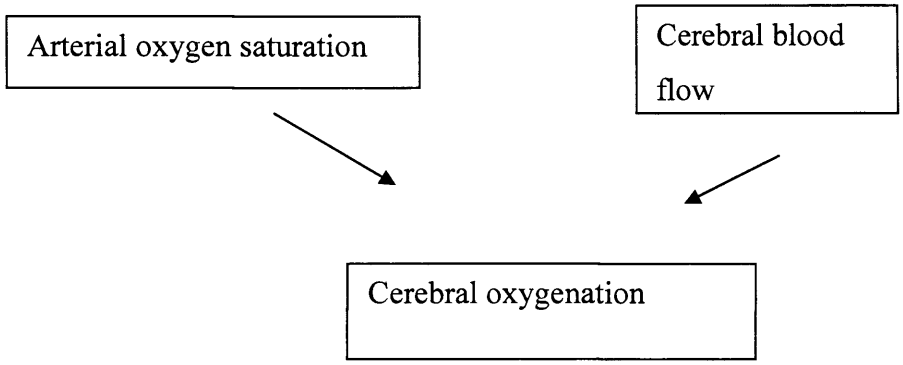
We also demonstrated that it is possible to estimate absolute CBV in hypoxic patients using oxygen challenge, where the previously described method involves induced hypoxia (154). The importance of CBV measurement lies in the fact that it is one of the only absolute measures available from NIRS, however its clinical significance is unclear. It may be relevant to ventilatory responses to changes in CO_2 in COPD patients. Variations in cerebral blood flow will alter the relationship between arterial pCO_2 and CO_2 tension at central chemoreceptors with the latter as principal determinant of ventilatory response (193). We obtained a mean CBV of 2.52ml/100g with a standard deviation of 0.69ml/100g. A previous study using an induced fall in SaO2 of <5% which is closer to the method originally described (154) measured CBV (ml/100g) of 2.41 ± 0.66 in normocapnic patients and 2.90±0.6 in hypercapnic patients with COPD (173). We did not demonstrate a relationship between pCO_2 and CBV in our patients but numbers were small and not all ABG measurements were contemporaneous. The variation in observed results may still be due to pCO_2. Accuracy of the results will be reduced because the technique assumes no change in CBV during oxygen challenge, and there probably are some changes in most subjects as evidenced by changes in total haemoglobin. Differences in smoking history may account for some of the observed variation in measured CBV because of the reduction in cerebral-perfusion related to smoking (179-181). The values obtained may vary because the technique is not reproducible. A study on reproducibility of the NIRS desaturation-resaturation measurement to measure CBV in healthy subjects performed 4 replicate measurements in each of 2 trials, one with and one without disconnecting the equipment (194). They found a coefficient of variation of 12.6% and 10.0% respectively in the two trials on a mean value of 3.60±0.82 ml/100g. The same group also obtain lower values in their COPD patients (173), which may be due to age and asymptomatic cerebrovascular disease secondary to smoking.

Compared to the work done on OSA, the pilot studies in COPD were limited and there is a risk that we may overestimate their importance. However because of the limited amount of data on NIRS in lung disease, and more particularly the novelty of the TOI saturation measurement, these observations in a different patient group are worthwhile.

14. CONCLUSIONS

14.1 DISCUSSION OF FINDINGS

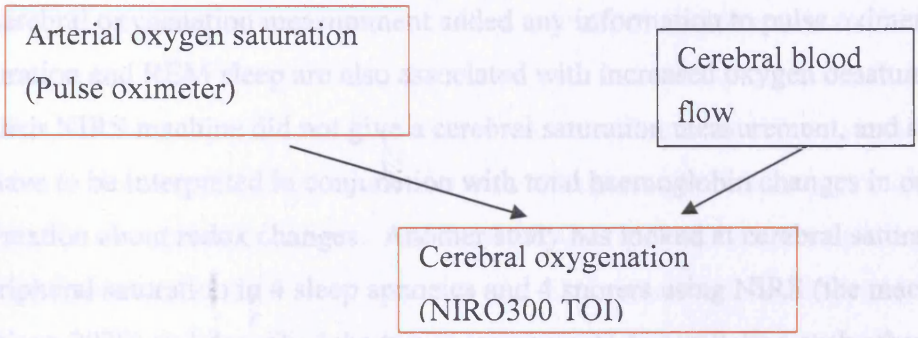
The work described in this thesis aimed to show that NIRS gives additional valid information when compared to measurement of arterial oxygen saturation alone in subjects with OSA and COPD. Cerebral oxygenation (tissue oxygen supply) depends on arterial oxygen saturation and cerebral blood flow, assuming oxygen consumption is constant.



In our validation studies we attempted to validate TOI as a measure of cerebral oxygenation in OSA. As described previously in the chapter on NIRS validation in general, there is no established non-invasive way of measuring cerebral tissue saturation from the region of interest. Hence we aimed to describe changes in TOI during OSA and show them to depend on SaO_2 and CBF.

14.1.1 First validation study – TOI and saturation

In the first validation study we looked at the relationship between arterial oxygen saturation and TOI in subjects with OSA.

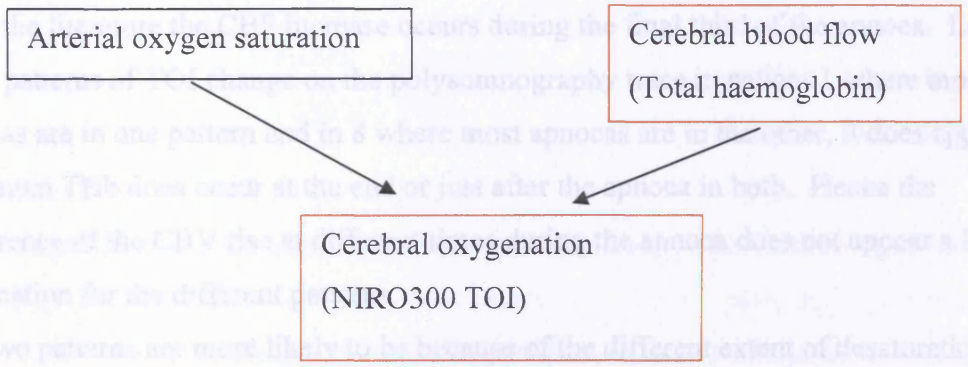


In 13 subjects with moderate to severe OSA we observed a reduction in regional cerebral tissue oxygenation index (TOI) during each obstructive apnoea and hypopnoea. The magnitude of the drop in cerebral tissue saturation during an obstructive event was related significantly to peripheral arterial SaO_2 drop, but, independently of this association, longer apnoeas and apnoeas occurring during REM sleep were also associated with greater drops in TOI. There was considerable variation between individuals in the change in TOI which occurred in response to a given saturation change. Mean event related dips in TOI ranged from 1.4 to 6.85%, where mean oxygen desaturation dips ranged from 3.8 to 22.3% in the 13 subjects. The clinical significance of small changes in TOI is not known, although as values of haemoglobin saturation in tissues are on the steep part of the haemoglobin dissociation curve, the corresponding changes in pO2 will be relatively large. Small changes in intracellular redox state may affect neurotransmitter metabolism (77). The mean change in TOI observed on clamping the internal carotid in the Cambridge validation study was –7.8% (111). Using a similar NIRS derived tissue saturation in subjects undergoing carotid endarterectomy under local anaesthetic, the mean saturation in 10 subjects who displayed neurological symptoms on clamping the internal carotid fell from 63.2+/-8.4% to 51 +/-11.6%, compared to 65.8+/-8.5% to 61.0 +/-9.3% in 90 subjects who were symptomfree (127).

There have been two previous studies measuring cerebral oxygenation using NIRS in OSA. The first established that changes in cerebral oxygenation occurred and that cerebral blood flow changes did not entirely compensate for saturation changes during apnoea (83). Like us they showed significantly greater falls in OHb in apnoeas during REM sleep and a significant relationship with apnoea duration. However they did not relate cerebral haemoglobin changes to oxygen saturation changes, and so were unable to conclude whether cerebral oxygenation measurement added any information to pulse oximetry, as apnoea duration and REM sleep are also associated with increased oxygen desaturation. In addition their NIRS machine did not give a cerebral saturation measurement, and so OHb changes have to be interpreted in conjunction with total haemoglobin changes in order to give information about redox changes. Another study has looked at cerebral saturation versus peripheral saturation in 4 sleep apnoeics and 4 snorers using NIRS (the machine was a Criticon 2020) and described the two measurements as paralleling each other, with cerebral saturation being 20-30% lower than peripheral saturation (84). They suggest that the difference between the values was due to the use of different monitoring techniques. Our results did not suggest parallel changes in peripheral arterial oxygenation and cerebral oxygenation, and this would not be predicted theoretically, because of cerebral blood flow changes. Their findings suggest a problem with the intracranial selectivity of their particular NIRS instrument, or with their analysis.

14.1.2 First validation study – cerebral blood volume and TOI

From the first validation study we had no direct measurement of cerebral blood flow so we used NIR total haemoglobin and calculated changes in cerebral blood volume as proxy measurements. There is considerable precedent for this in previous NIR literature (83).



In the 8 subjects from the initial validation study who had sufficient consecutive apnoeas for analysis, we observed significant correlations between the magnitude of changes in cerebral oxygenation measured as TOI and changes in CBV, as well as between TOI dip duration and both CBV and Cytox changes. We observed two patterns of temporal relationship between changes in cerebral blood volume and TOI: in some apnoeas the THb peak coincided with TOI minimum and in others with TOI maximum. Reduction in perfusion may explain the correlation in apnoeas in which TOI minimum and CBV minimum coincide. However the effect of CBV change on TOI change is significantly greater in the second pattern, where CBV maximum coincides with HHb maximum and TOI minimum. This suggests that the CBF increase itself may be worsening cerebral oxygenation if it occurs when arterial blood is poorly saturated and causes an influx of relatively deoxygenated blood.

If we ignore the complexities of the time relationships, the simple correlations between CBV changes and TOI changes support the basic hypothesis in the above figures. However the possibility that a surge in CBF at a time when arterial blood is at a saturation of around 60 or 70% might have an adverse effect on cerebral oxygenation is entirely plausible.

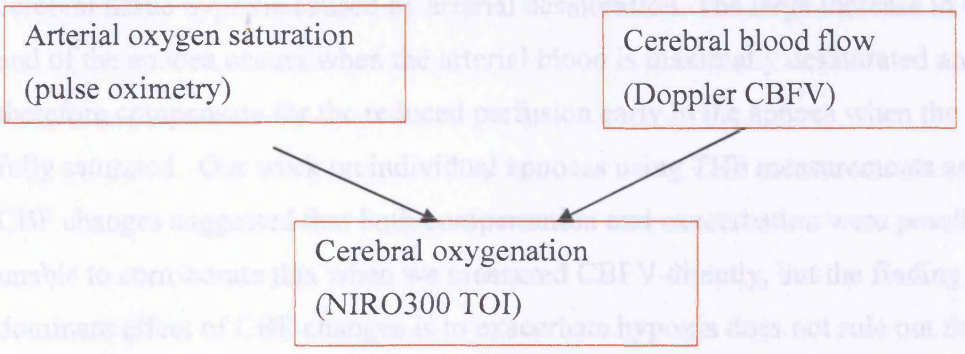
The two temporal relationships between changes in THb and TOI were seen in the same patient as well as in different patients. These two relationships can be explained by whether oxygenated haemoglobin was rising or falling during the THb rise (OHbratio). Where the CBV increase occurs while oxygenated haemoglobin is rising, we can assume that the incoming blood is relatively oxygenated, and when OHb falls during the CBV rise, that the incoming blood is relatively deoxygenated. We did not have the facility to look at THb measurements synchronised with polysomnography measurements of apnoea to establish whether the THb rise always occurred at the same time relative to the apnoea. From the literature the CBF increase occurs during the final third of the apnoea. Looking at the patterns of TOI change on the polysomnography trace in patient 1 where most apnoeas are in one pattern and in 8 where most apnoeas are in the other, it does appear that maximum THb does occur at the end or just after the apnoea in both. Hence the occurrence of the CBV rise at different times during the apnoea does not appear a likely explanation for the different patterns.

The two patterns are more likely to be because of the different extent of desaturation during apnoea in different subjects. The extent to which incoming blood is deoxygenated

at the time of the CBV increase will depend on length of apnoea and rate of desaturation. Both of these variables have been extensively researched in OSA. Apnoea termination may be triggered by chemoreceptors or mechanoreceptors (137). Rate of desaturation will depend on underlying lung disease, lung volumes or occurrence of apnoea in inspiration or expiration (135, 195). REM sleep stage will affect apnoea duration and extent of desaturation, and may explain the differences seen. Patient 1 was in REM sleep for some of the section analysed, and patient 8 had no REM sleep during his recording.
We are left with no more than an interesting idea about the ways that arterial saturation changes and cerebral blood flow changes could combine during apnoea to produce differing effects on cerebral oxygenation. Unfortunately this idea is based on interpretation of total haemoglobin changes as blood flow changes, and even though in later pilot studies we measured CBFV changes using Doppler, we still had no more sophisticated way of measuring the oxygenation of the incoming blood than using simple NIR OHb and HHb measurements during the THb rise. The observation of the two time relationships is new and was not commented on by Hayakawa (83) who only illustrated one trace. Overall this work supports the hypothesis that TOI measurement gives more information than that available from arterial saturation alone.

14.1.3 Second validation study – CBFV, arterial saturation and TOI

In the second validation study we looked at the interrelationship of SaO_2, CBFV and TOI.



We demonstrated both quantitative and temporal correlations between changes in CBFV and changes in cerebral tissue saturation measured as TOI in 7 patients. The relationship between CBFV and TOI remained significant after SaO_2 was included in the regression equation. In one subject who had isolated CBFV changes, TOI changes accompanied

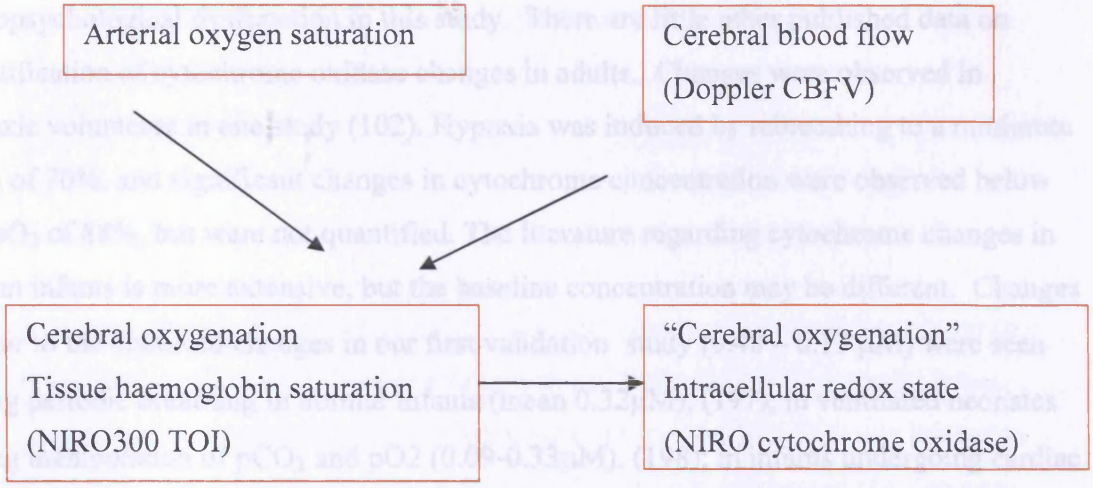
these CBFV changes and correlated in amplitude with them, but not with ABP or SaO_2 changes. We therefore showed that the changes in SaO_2 and in CBFV both influence cerebral oxygenation in obstructive sleep apnoea.

During obstructive sleep apnoea cerebral blood flow is reduced by the reduction in intrathoracic pressure, and then increases towards the end of the apnoea due to blood gas changes and autonomic arousal. It is known that this mixture of passive and autoregulatory blood flow changes does not fully compensate for the oxygen desaturation during apnoea (1, 83). It is unclear from previous literature whether the dominant effect of the CBFV changes on cerebral oxygenation is to compensate for or exacerbate the hypoxia caused by arterial desaturation. A previous NIR study found an increase in total haemoglobin during apnoea, despite reduction in cerebral oxyhaemoglobin, (83), which was interpreted to mean that CBF changes incompletely compensated for SaO_2 changes. A second study also found a predominant increase in CBFV during the desaturation (24). Reduced perfusion during apnoea was found in other studies (18, 22). In 2 studies where changes during individual apnoeas were not resolved, reductions in CBFV (19) and in CBF measured using inhaled xenon 133 (25) were observed during sleep in OSA subjects compared to control subjects. For the first time in this study we have been able to measure cerebral oxygenation simultaneously with SaO_2 and CBFV, and have shown that despite a partial compensatory effect of the CBFV increase at the end of apnoea (visible in Figs 39 and 40), a bigger change in CBFV is associated with a bigger drop in TOI in the multiple regression. This suggests that the overall effect of the CBFV changes is to exacerbate the cerebral tissue hypoxia caused by arterial desaturation. The large increase in CBFV at the end of the apnoea occurs when the arterial blood is maximally desaturated and may not therefore compensate for the reduced perfusion early in the apnoea when the blood is more fully saturated. Our work on individual apnoeas using THb measurements as proxy for CBF changes suggested that both compensation and exacerbation were possible, we were unable to corroborate this when we measured CBFV directly, but the finding that the dominant effect of CBF changes is to exacerbate hypoxia does not rule out the fact that some compensation may also occur.

One subject had repetitive changes in CBFV during sleep associated with changes in TOI and ABP, without changes in SaO_2. This subject was known to be a snorer with mild OSA (dip rate 16), but did not demonstrate obstructive events during this daytime nap of 52mins. CBFV changes in this subject may have been due to upper airway

resistance and associated arousals. These changes in cerebral oxygenation would have been missed by isolated pulse oximetry monitoring. It is possible that upper airway resistance syndrome (UARS) may cause changes in cerebral oxygenation because of changes in CBFV associated with intrathoracic pressure changes and arousal. Further investigation is necessary to find out whether these changes in cerebral oxygenation are clinically relevant.

14.1.4 Intracellular redox changes

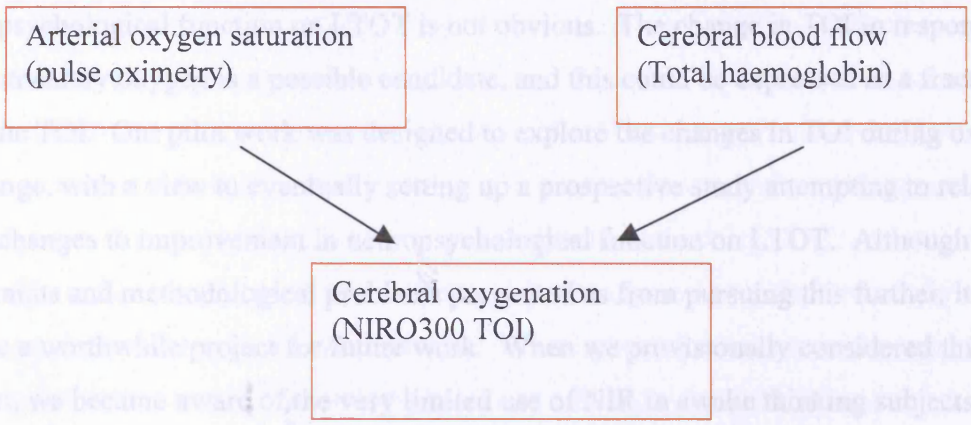


In order to examine the metabolic effects of tissue hypoxia in OSA we looked at changes in cytochrome oxidase redox state in relation to tissue saturation of haemoglobin with oxygen (TOI), SaO_2 and CBFV. Cytochrome oxidase can be seen as the enzyme responsible for the conversion of oxygen to water, or simply a reflection of mitochondrial oxygen availability, relevant to other intracellular enzyme systems.

Changes in cerebral cytochrome oxidase redox state during apnoea using near infra-red spectroscopy were observed during 15 episodes of daytime sleep in subjects with moderate to severe OSA. The magnitude of these changes varied from 0.08 to 0.48μM. Changes in cytochrome oxidase correlated with changes in brain tissue saturation measured as TOI, as well as with peripheral arterial oxygen saturation and cerebral blood flow velocity changes. The observed quantified changes in cytochrome redox state were small. Absolute adult human cytochrome oxidase concentration is not known but it was found to be 5.5μM in the adult rat (196). The adult human has a lower cerebral oxygen consumption rate than the rat so this value would be expected to be the upper limit of the concentration in humans

(153). Hence our observed changes are between 1 and 10% of the predicted total concentration. Cerebral blood flow changes will have little effect on the baseline concentration as red blood cells do not contain mitochondria. Therefore the absolute cytochrome oxidase concentration is unlikely to change in the timescale of our recordings and so these changes can be interpreted as redox changes. In the only study looking at cytochrome oxidase changes and neuropsychological function in 41 adult subjects undergoing cardiac surgery with cardiopulmonary bypass, the 4 subjects who had marked cognitive deficit post operatively had a mean maximum fall in cytochrome oxidase oxidation of 4.5μM (124). No other measured parameter significantly predicted neuropsychological dysfunction in this study. There are little other published data on quantification of cytochrome oxidase changes in adults. Changes were observed in hypoxic volunteers in one study (102). Hypoxia was induced by rebreathing to a minimum SaO_2 of 70%, and significant changes in cytochrome concentration were observed below an SaO_2 of 88%, but were not quantified. The literature regarding cytochrome changes in human infants is more extensive, but the baseline concentration may be different. Changes similar to the observed changes in our first validation study (0.48 – 0.13 μM) were seen during periodic breathing in normal infants (mean 0.32μM), (197); in ventilated neonates during manipulation of pCO_2 and pO2 (0.09-0.33μM), (198); in infants undergoing cardiac surgery (1.14μM assuming infant DPF of 3.85), (199) and in infants receiving indomethacin for treatment of patent ductus arteriosus (0.18-0.92μM), (200). These 4 studies illustrate that changes in cerebral haemodynamics, pCO_2 and to a lesser extent pO2 are associated with small changes in cytochrome oxidase redox state in infants, but in none of these studies were the subjects followed up to look for physiological consequences of these changes. The study on adults quoted above (124) showed neuropsychological consequences of much larger changes. The clinical significance of smaller changes is unknown.

14.1.5 NIR in chronic hypoxia



In subjects with chronic hypoxia due to COPD it was possible to look at the relationship between cerebral oxygenation, total haemoglobin and SaO_2 during oxygen challenge. From the point of view of validating the NIRO300, we showed that TOI was related to both total haemoglobin and SaO_2. From a clinical viewpoint we showed that the same increase in SaO_2 did not always result in the same percentage increase in cerebral saturation, and that THb (and presumably CBF) changes accounted for some of the discrepancy.

Although the TOI is a tissue saturation, it clearly depends to a great extent on cerebral haemodynamics, and this makes it a particularly appropriate tool for the study of OSA, where there are changes in CBF occurring every apnoea, and probably less appropriate for study of chronic hypoxia, where there may be chronic compensatory mechanisms maintaining cerebral oxygen delivery (polycythaemia, 2,3DPG changes, changes in CBF). Monitoring of stable patients will give little information, and responses to oxygen challenge are difficult to interpret without simultaneous monitoring of pCO_2 and absolute CBF. Our pilot work in this patient group was very limited. Other groups have looked at the measurement of CBV in COPD, and cerebrovascular reactivity using NIR(173), in an attempt to define whether subjects with increased pCO_2 have a different cerebrovascular response to changes in pCO_2. There has been little work on the effect of supplementary oxygen on cerebral oxygenation, or the clinical relevance of cerebral oxygenation

measurement. This issue is of interest because the original LTOT trials showed benefit of supplementary oxygen particularly in people with neuropsychological dysfunction (159, 160). Because baseline TOI is so variable in different people, the measurement derived from TOI which would be appropriate for comparison in a prospective study of neuropsychological function on LTOT is not obvious. The change in TOI in response to supplementary oxygen is a possible candidate, and this could be expressed as a fraction of baseline TOI. Our pilot work was designed to explore the changes in TOI during oxygen challenge, with a view to eventually setting up a prospective study attempting to relate these changes to improvement in neuropsychological function on LTOT. Although time constraints and methodological problems prevented us from pursuing this further, it would still be a worthwhile project for future work. When we provisionally considered this project, we became aware of the very limited use of NIR in awake thinking subjects, where thought processes may cause changes in regional blood flow picked up by NIR. Most work has been carried out on ITU or in the operating theatre where subjects are unconscious, and there is a growing interest in the use of NIR for functional imaging, where the purpose is to pick up regional blood flow changes during cerebral activity. Thus the assumption that local frontal cerebral oximetry is representative of global changes may break down in awake subjects and thus NIR may be easier to interpret in asleep subjects with OSA than awake subjects with COPD.

14.2 LIMITATIONS OF THE RESULTS IN THIS THESIS

14.2.1 Validation

Problems with validation with NIRS lie not in its validation as an oximeter, but with its validation as a cerebral oximeter. The diagrams of reflectance spectroscopy with light traveling across the scalp, skull, meninges, skimming the surface of the brain tangentially and then battling its way out the other side make it difficult to believe that the predominant tissue sampled is brain. There is a much cited article showing that a different NIR machine sampled predominantly extracerebral tissue (201). Use of near infrared spectroscopy as a cerebral oximeter assumes that (a) it is imaging brain and (b) the local changes in cerebral oxygenation represent global changes occurring in response to a global hypoxaemic or haemodynamic challenge. Spatial resolution of NIRS is poorly defined and the NIRO300

is no exception. Because it purports to measure regional cerebral oxygenation, direct validation (for example against jugular bulb saturations) is not possible, and the only current validation study for the NIRO300 uses its response to alterations in intracerebral and extracerebral blood flow. Using sequential clamping of internal and external carotids in 60 patients during carotid surgery, TOI changes were seen in 49 subjects; during external carotid clamping in 8, and during internal carotid clamping in 41. TOI correlated significantly with cerebral blood flow velocity (r=0.56) but not with cutaneous laser-Doppler flowmetry (r=0.13). Discounting the 8 subjects in whom clamping the external carotid affected systemic blood pressure and CBFV, the sensitivity of TOI to intracranial and extracranial changes was 87.5% and 0% respectively, and specificity was 100% and 0% respectively (111). Hence the NIRO300, certainly in this clinical context, appears to be selective for intracranial blood flow changes.

The second assumption, that local changes are representative of global ones, holds provided that the subjects have no focal cerebral disease, and that there is no focal stimulation of parts of the cortex. This assumption probably holds true for the OSA subjects, who had no history of cerebrovascular disease, and were asleep during the recordings. Cerebrovascular disease cannot be ruled out on history alone. Davies et al (72) found MRI findings consistent with cerebrovascular disease in OSA patines and normal controls. As we measured changes in TOI during individual apnoeas from a moving baseline, any regional changes in cerebral blood flow during sleep would only affect the interpretation of our findings if they occurred on a timescale of individual apnoeas. Regional abnormalities in CBF including frontal hyperperfusion have been shown in subjects during periods of apnoeas, using SPECT imaging (202). However the time resolution of this technique is not sufficient to show whether there are regional cerebral blood flow changes during individual apnoeas. As the COPD subjects were awake regional blood flow changes may have occurred due to cerebral activation during the oxygen challenge and may account for the different THb changes during the challenge. This possibility does not affect the demonstration of the responsiveness of TOI to both SaO_2 and THb changes.

14.2.2 TOI variability and reproducibility

Baseline TOI measurements are variable despite similar baseline arterial oxygen saturations, both in our study and in 60 subjects undergoing carotid endarterectomy (mean

baseline TOI 67.8% (SD=8.8, range 49 - 93) (111). Table 65 illustrates baseline TOI saturations from the available literature on NIRO300.

Table 65. Baseline TOI values from studies using NIRO300

TOI = tissue oxygenation index

Number of subjects	*Mean baseline TOI*	*SD*	*Range*	*Reference*
60	67.8		48.7-93.0	(111)
30			48-85	(119)
10	64.9	5.1		(121)
19	66	8		(122)
13			50.2-75	(1)
7	73.2		60.8-84.0	(203)
56	66.5		43.3-78.8	Our study OSA subjects

This variability seems to upset chest physicians who see cerebral oxygenation measurement as a similar type of measurement to arterial saturation more than neurosurgeons, who see it more as a haemodynamic measurement. Cerebral oxygenation depends on cerebral blood flow as well as SaO_2, and the 60 neurosurgical subjects also demonstrated a range of middle cerebral artery flow velocities. In addition the relative arterial and venous contributions to the signal vary from person to person and with site (204). Local blood flow variations, changes in tissue oxygen consumption and global cerebral blood flow changes will introduce variability in the signal from one subject over time. Factors affecting variability in INVOS 4100 cerebral saturation were examined in 111 anaesthetised patients and age, haemoglobin concentration and probe position were found to affect rSO2 values (205). There were no significant correlations with weight, height, head size and sex. The relation with age may well be true, as it also occurs with SaO_2, and the different algorithms mean that the association with haemoglobin concentration may well not hold true for the NIRO300. A similar study has not been published for NIRO300, however our experience showed that head curvature had a definite effect on TOI, as the algorithm assumed a fixed intra probe distance of 4 or 5 cm which would be reduced by curvature. Apart from this, in the absence of a way of independently

measuring cerebral oxygenation, it is difficult to say that TOI variations with probe position are not true. Because of the baseline variability some groups report changes in cerebral saturation as a fraction of the baseline values (127), and others report absolute changes (111). Clearly if the baseline variability is not artifactual but true, then the absolute changes are more physiologically relevant, and on this basis we used absolute rather than fractional changes in our analysis.

14.2.3 Interpretation of cytochrome oxidase

The extent to which cross talk between the haemoglobin signals and the cytochrome signal affects cytochrome oxidase results is ill defined. The two signals can be distinguished in animal studies (129, 206), but in in vivo studies it may be difficult to be certain that an observed change is not artifact, especially if it is small and occurs at the same time as a large change in one of the haemoglobins (153). Cytochrome oxidase changes due to hypoxia have been shown experimentally to occur at saturations in the region of 50% (128), but the reduced SaO_2 in OSA may be compounded by reductions in CBF. Our observed changes may not be due to cross talk because their magnitude is within a physiologically appropriate range, they occur in association with significant oxygen desaturations, and they do not show precise temporal correlation with OHb or HHb. Because the cytochrome measurements are made relying on basic NIRS and not spatially resolved spectroscopy, they are more likely to suffer from significant extracranial contamination. Luckily however mitochondria are absent in red cells, so that the signal is unlikely to be significantly contaminated by the extracranial blood flow changes that occur during apnoea. Total haemoglobin measurements are similarly liable to extracranial contamination and will be affected by blood flow changes, so that where there is a discrepancy between changes in THb and in CBFV, the latter are assumed to be correct. In fact wherever the cytochrome changes are coming from, their very existence suggests an effect of sleep apnoea on mitochondrial metabolism, which is a new finding whether or not some of the signal is coming from mitochondria in extracranial tissues. Worries about spatial resolution thus take second place to worries about the relevance of small cytochrome changes occurring at the same time as large haemoglobin changes. Lack of confidence in interpretation has meant that the cytochrome signal in adult studies is frequently ignored. Our changes are biologically plausible, and it seems that only by

reporting cytochrome changes more frequently in adults, can we come to understand their physiological significance.

14.2.4 Size of changes

The size of the changes in TOI and cytochrome oxidase are small, compared to those observed in animal studies and in subjects undergoing cardiopulmonary bypass. However our collaborators working on NIRO were keen to work on OSA because of the size of the spontaneous desaturations in some subjects. In cytochrome work it is difficult ethically to induce desaturation to the extent that cytochrome changes are observed in humans. Much of the NIRO validation has been done on subjects undergoing carotid endarterectomy, where clearly the aim is to avoid cerebral desaturation due to internal carotid clamping on which TOI validation is based. Increasingly subjects in whom this desaturation is likely, are undergoing intraoperative shunt procedures prior to clamping so these NIRO studies can no longer be carried out. The repeated nature of apnoeas also provides multiple replications of events for analysis. All traces were analysed manually and visualized graphically, as is the norm with polysomnography. Hence we are in no doubt that the changes observed, although small, are apnoea related rather than due to noise. Whether or not these repetitive changes are associated with clinical outcome was not the subject of this pilot work.

14.2.5 Appropriate summary measures

In order to perform a study to see if measurement of TOI predicted neuropsychological function in subjects with OSA, it was necessary to measure TOI during full overnight polysomnography, and derive some output from the TOI trace that could be compared between subjects. We faced the problem that if our study showed no relationship between TOI and neuropsychological outcome, this could be due to the use of the wrong summary measure, and would not necessarily negate the hypothesis. We should remember that clinical validation of sleep study measures has rarely been performed, and most are validated against AHI, which itself is poorly correlated with symptoms. The area under the curve and dip rate calculations both had limitations. Both were calculated assuming TOI as an absolute measure, ie that 1% change in TOI is equivalent in all subjects and does not

need to be corrected for baseline. If this were false it would affect the AUC measurements more than the dip rates. The TOI trace was noisier than the saturation in some subjects. AUC measurements picked up all variations including movement artifact, and because the digital output was not recorded simultaneously with the poly it was not possible to remove periods of wake from the recording. The maximum baseline value was defined arbitrarily as the value that 99% of observations were below, and clearly an error of 1% in this would make a big difference to the final values. It is known that sleep studies vary considerably from night to night and that the first night is often not representative of the average. Because of our limited resources we were not able to perform more than one night study for each subject. Somewhat inevitably we ended up comparing subjects who had only slept for 3 hours to others who slept for 10 hours, and subjects who displayed no REM sleep with those that did. The dip rate calculations were performed manually from the poly trace and therefore were apnoea associated rather than computer calculated dips. They were therefore less subject to noise than the AUC measurements. We plan to repeat analysis using measurements corrected for baseline TOI.

14.2.6 Sleep disruption and arousal.

One of the main stimuli to blood pressure changes and thus to CBF changes during apnoea is the autonomic arousal. It is possible that the CBF changes are an epiphenomenon of arousal, and that their effect on symptoms due to their effect on cerebral oxygenation is trivial, compared to the effect on symptoms caused by sleep disruption. We may be kidding ourselves that by using NIRO we are looking at the effect of cerebral oxygenation independent of sleep disruption, when in fact the contributions of hypoxia and arousal to sleep apnoea symptoms are as inseparable as ever. It has been recently shown for hypertension that the arousal related swings at night are associated with daytime blood pressure changes (42), and so it remains possible that CBF changes may affect symptoms independent of arousal.

14.3 MAIN FINDINGS

The main new findings from this experimental work are the following:
NIRO TOI responds to changes in both CBF and SaO_2 in OSA.

The changes in cerebral blood flow that occur during obstructive apnoea tend to exacerbate rather than compensate for arterial desaturation, ie thay cannot be viewed as a predominantly homeostatic mechanism.
Changes in intracellular redox state, exemplified by changes in cytochrome oxidase oxidation state, occur during OSA in some patients.
The last two findings contribute new information to the understanding of the pathophysiology of obstructive sleep apnoea.

14.4 CLINICAL SIGNIFICANCE.

The ultimate test of the usefulness of measurement of cerebral oxygenation using NIRO300 in subjects with obstructive sleep apnoea will come from the results of the prospective study using overnight NIRO measurements in association with objective neuropsychological testing before and after treatment. Our validation and pilot work described in this thesis established that the NIRO measurement picked up changes in both CBFV and SaO_2 during obstructive sleep apnoea, and so would be expected to provide more information about cerebral oxygenation than pulse oximetry alone. As so many of the symptoms of OSA are neuropsychiatric we would expect measurement of cerebral oxygenation to be relevant to symptomatology. We derived summary TOI measures for sleep studies and validated them against AHI as is conventional. We planned to use these TOI measures with conventional polysomnography variables in multiple regression with neuropsychology score as an outcome.
The work on cytochrome oxidase has perhaps the most potential, as illustrating an intracellular effect of tissue hypoxia, and also providing a human model of repetitive cytochrome changes, which we assume occur because of simultaneous changes in CBF and SaO_2 (as the saturation changes alone are probably insufficient to affect cytochrome oxidation state on the basis of previous experimental work). We collected cytochrome data on all the overnight sleep studies for the prospective neuropsychological study. Unfortunately it was much more difficult to calculate an overnight cytochrome score than a TOI score, comparable between subjects, because of the arbitrary baseline as well as drift and noise. Ideally we would aim to enter an overnight value into multiple regression with neuropsychological score as outcome, to see if the cytochrome measurements predict

outcome better than TOI. With the help of Medical Physics at UCL we hope that some cytochrome analysis from the prospective study may be performed in the future.
Work on chronic hypoxia was more limited, but we were able to show changes in cerebral blood volume occurring acutely in response to oxygen, which may influence the effect of supplementary oxygen on cerebral oxygenation. Again neuropsychological improvement associated with increased survival was seen in the original trials of long term oxygen therapy.
Future work on chronic hypoxia could include a study of whether the TOI response to oxygen challenge predicts neuropsychological improvement using LTOT. We thought of performing neuropsych tests on and off oxygen, but the use of NIRO300 in this context could confuse its role as a cerebral oximeter with that as a measure of cerebral activation. Overall OSA proved itself more appropriate for study with NIRO because of the cerebral haemodynamic changes occurring with each apnoea.

14.5 PERSONAL VIEW

Learning to use and understand the technology of near infra-red spectroscopy in this project was an exciting "voyage of discovery" for me involving many disciplines previously little known to me. From a background of respiratory medicine with an intercalated degree in biochemistry, I extracted papers from journals in neurology, neuropsychology, neonatology, cardiothoracics, anaesthesiology, and medical physics, and visited the National Hospital for Neurology and Neurosurgery at Queen Square, neurosurgical theatres at Addenbrookes, as well as holding discussions at UCL with people in Medical Physics and Paediatrics, where the prototype NIRO was developed, and then in the Dept of Health Psychology to develop the protocol for the neuropsychological validation study. I had no idea when I first started the project how controversial the technique of NIRS was, and of how much argument surrounded each measurement. I started with the clinician's idea that if you connect a machine to a patient and a number comes up, then that number is a valid measure of whatever the machine claims to measure, provided it is properly connected. I gradually learnt about how a new measurement technique is validated, of the statistical techniques used (and the correct interpretation of simple correlations), and of the mysteries of calibration and analogue to digital converters.

I learnt to appreciate just how much data the average sleep study computer is able to analyse for a single sleep study, and to understand why it took so many years and computer advances between the discovery of the EEG and a full night polysomnography. I learnt the advantages and disadvantages of computer algorithms for eg dip rate analysis, and have now a much better ability to interpret sleep study results, after being forced to use manual analysis for the NIRO.

The future of NIRS is still unclear in the literature, even 5 years on from when we started working with it. It is still a way away from being a routine intraoperative or ITU monitoring tool. Using it in sleep apnoea was relatively easy, and to our surprise we were able to leave it on unsupervised overnight without major problems. Because of repetitive changes in SaO_2 and CBF, and because of prominent neuropsychological symptoms, unexplained by current markers of severity, OSA seems an ideal clinical scenario in which to test the clinical relevance of NIRS measurements. The theory behind the method is elegantly simple, and I have been lucky to meet a few enthusiastic "believers" in it, who spurred me on to complete this thesis.

At the time we received our NIRO300 there was only one published paper using it. In a way I feel privileged to have had to assimilate myself the necessary knowledge and contacts to be able to use this new and complex instrument in a properly designed and piloted study. I am sure that the knowledge I have acquired about medical instrumentation, sleep studies, and design of a clinical study will be useful in my future career as a chest physician with special interest in sleep and respiratory failure.

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FIGURE ACKNOWLEDGEMENTS

Figures 4, 12 and 14 were obtained from Google Images. References are http://fig.cox.miami.edu/~cmallery/150/makeatp/c9x15chemiosmosis.jpg for Figure 4; www.hitachimed.com/graphics/products/ optical_measurement.asp for Figure 12; and medicalteknikajp.hp.infoseek.co.jp/ cerebral/Niro300 for Figure 14. All were last accessed on 13/9/05. The photographs reproduced in Figures 6, 7 and 8 were taken by Himender Makker with permission from the subjects. Figure 13 is the property of Hamamatsu. Figure 15 was drawn for me by Sam Harris. The graphs reproduced in Figures 34 to 38 were redrawn for me by Clare Elwell. Figures 1,3,9,10 and 11 are acknowledged in the text.

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APPENDIX

CONTENTS

EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in the last few weeks. Even if you have not done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation.

0 = Would never doze

1 = Slight chance of dozing

2 = Moderate chance of dozing

3 = High chance of dozing

Situation	**Score**
Sitting and reading	
Watching television	
Sitting inactive in a public place (eg a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down in the afternoon, when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
Driving a car, while stopped for a few minutes in the traffic	

Total = ...

Sample recruitment letters for second validation study

UNIVERSITY COLLEGE LONDON HOSPITALS

DEPARTMENT OF THORACIC MEDICINE
The Middlesex Hospital
Mortimer Street, London W1N 8AA

Dear

I am writing to let you know about a research study which is taking place at the Middlesex Hospital and to invite you to take part. It would involve you coming up to Campbell Thompson Ward during the day, having some monitors attached, and going to sleep for an hour or two. If you are on CPAP treatment you would have to stop using it for one or preferably two nights before the study so you are able to sleep during the day. We are aiming to find out more about how obstructive sleep apnoea, the condition you suffer with, affects the supply of oxygen to the brain. We are using a machine that can measure brain oxygenation by measuring light changes through the skull and a second machine that measures blood flow using an ultrasound technique. There are no known adverse effects from these machines.

The study will be taking place on 29th September and 2nd to 6th October. I will try to contact you by phone nearer the time see if you are interested in helping us and to confirm a time if you are. If you would like more information, would like to arrange a time, or wish not to be contacted further, please fill in the attached slip. Alternatively you can ring the lung function lab on 9243.
Thank you,

Yours sincerely

Dr Anne McGown (Research Registrar to Prof Spiro)

✂ .....

I would like more information ☐

I would like to take part. The day that would suit me best is .....

I would prefer morning ☐ or afternoon ☐

I am willing to stop using CPAP one/two nights before ☐

I would prefer not to be contacted further in relation to this study ☐

Please return to Dr Anne McGown at the above address. I am away until 17th September but will be able to contact you the week after that to confirm dates.

UNIVERSITY COLLEGE LONDON HOSPITALS

DEPARTMENT OF THORACIC MEDICINE
The Middlesex Hospital
Mortimer Street, London W1N 8AA

UCL HOSPITALS

Ann-Marie Dempsey

Dear

Thank you for offering to take part in our study on the impact of obstructive sleep apnoea on brain oxygenation.

Please can you attend on Campbell Thompson ward at …….. on ..... where I will be meeting you.

We will be connecting you to some monitors and then asking you to go to sleep for one or two hours. Please allow for spending 3-4 hours in total in the hospital. We would like you not to use your CPAP machine if you have one for **at least one and preferably 2 nights** prior to the study, so that you will be able to sleep during the day. I enclose an information sheet about the study.

If there are any problems with this date or if you have any further questions, please can you contact me on 020 7636 8333 Ext 4135 or Kanta on 7380 9243. Please say if you wish to change or cancel the appointment. We are running the study from 29th September until 6th October.
I am away until the 17th September but will try and phone to confirm with you the week after that.
Thank you for your help and I look forward to seeing you.

Your sincerely

Dr Anne McGown (Research Registrar to Prof Spiro)

Patient information for second validation study

Impact of obstructive sleep apnoea on cerebral oxygenation measured by near infra-red spectroscopy – validation pilot study.

PATIENT INFORMATION LETTER

You are being asked to take part in a study looking at a new way of measuring brain oxygenation in people with sleep disordered breathing.

You have a condition called obstructive sleep apnoea which may cause you problems with memory and concentration. Your condition was diagnosed by measuring the oxygen levels using a probe on the finger. We have a new technique now that measures oxygen levels in the brain through the skin and we think this may be better. Last year we studied this new technique alongside the old one in some subjects with your condition and measured the changes in brain oxygenation while they were asleep. Now we would like to make sure these changes really are coming from the brain using some other monitors that we will describe below.

We would like you to come up to the sleep side room at the Middlesex Hospital for half a day so that we can monitor you while you have a nap. If you are on CPAP we will ask you not to use it for 2 days before, so you are more likely to sleep during the day. The monitoring we will use consists of the following probes.

1. We will be using a technique called near-infra red spectroscopy to assess brain oxygenation. This involves shining invisible (infrared) light about as bright as a torch beam across the head. By measuring changes in the light absorbed it is possible to estimate changes in brain oxygenation. You will have 2 leads attached to your forehead using a self adhesive sticker and a cloth band. Measurements are entirely painless, but occasionally the site gets a little red if the probe is on for a long time. There are no other side effects.
2. We will use a probe just in front of your ear that picks up signals about blood flow to the brain using an ultrasound technique. This is called transcranial Doppler ultrasound.
3. We will use another Doppler ultrasound probe on your forehead to monitor skin blood flow.
4. We will measure changes in oxygen saturation levels using a probe on your finger.
5. We will measure changes in blood pressure also from a probe on your finger.
6. We will monitor airflow using a probe close to your nose.
7. We will monitor how deeply asleep you are using some little probes stuck on your head with tape or glue.

None of the monitoring equipment has any side effects or causes more than mild discomfort.

We will ask you to lie down and go to sleep if you can for 1 to 2 hours. We will then take off the equipment and you will be able to leave. We will collect the information from the monitors and use it to validate the new technique.

If you agree we also do a routine blood test to measure haemoglobin which is the substance that carries oxygen in the blood.

If you have any questions either now or at any time please ask. Your participation in the trial is entirely voluntary and if at any time you wish to stop taking part you may do so. This will not affect your subsequent clinical care in any way.

You can contact the investigators, Dr Makker or Dr McGown, by leaving a message with the lung function lab (0171 380 9243) or on voice mail (0171 636 8333, ext 4135), and we will return your call as soon as we can.

All proposals for research using human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the Joint UCL/UCLH Committees on the Ethics of Human Research.

Sample GP letter for prospective study

STUDY OF NEUROPSYCHOLOGICAL DYSFUNCTION IN OBSTRUCTIVE SLEEP APNOEA

Dear GP

Thank you for referring your patient for investigation of possible sleep disordered breathing. We are currently running a study of neuropsychological performance in obstructive sleep apnoea in collaboration with the department of Psychiatry and Behavioural Science, University College, London. All new referrals are being invited to participate in this trial. If they consent, they will all have a set of neuropsychological tests performed prior to their screening sleep study. Following their sleep study, simple snorers will have a further set of neuropsychological tests performed after about a month, and will have appropriate treatment arranged in the usual way. People with obstructive sleep apnoea (OSA) will have polysomnography performed with cerebral oxygenation measurement using near infra-red spectroscopy (NIR). This technique measures cerebral oxygenation non-invasively by transmitting NIR light through tissue and measuring changes in the absorption spectra of the haemoglobins and cytochrome oxidase. Following the polysomnography all patients with OSA will be offered continuous positive airway pressure (CPAP) therapy. After a month of treatment, neuropsychological testing, polysomnography and cerebral oxygenation measurement will be repeated on treatment. Following the study, they will be managed under the sleep clinic at Grays Inn Road in the usual way.

The mechanism of neuropsychological dysfunction in OSA is not known, and our study will allow us to correlate direct measures of cerebral oxygenation with results of cognitive testing. We hope that the information we obtain will help in making decisions about which patients with sleep disordered breathing should be treated. We will be offering CPAP to all patients with OSA in the study, on the basis of a trial by the Edinburgh sleep research group which showed improvement in neuropsychological function even in mild OSA after 28 days CPAP treatment. Following the study, alternative treatment options including oral appliances will be available to patients as usual.

If you have any further questions please do not hesitate to contact us.

Yours sincerely

Dr H Makker

Consultant in Respiratory Medicine

Patient information letter for prospective study

STUDY OF NEUROPSYCHOLOGICAL DYSFUNCTION IN OBSTRUCTIVE SLEEP APNOEA

PATIENT INFORMATION LETTER

You are being asked to take part in a study looking at memory and concentration in people with sleep disordered breathing.

You are being investigated for a condition called obstructive sleep apnoea. In this condition people have repetitive collapse of the upper airway during sleep, causing a fall in oxygen reaching the brain, which is ended when the person jerks awake and starts breathing again. The main symptoms consist of snoring, disturbed sleep and daytime sleepiness, but some people also notice problems with memory, concentration and ability to think. We don't know what causes these problems, but we do know that they may be improved by treating even mild forms of obstructive sleep apnoea. We would like to find out how the lack of oxygen reaching the brain at night affects thought processes during the day and so we are asking you to take part in this study.

If you agree to take part, we will do two blood tests (full blood count and thyroid function tests) and a lung function test (involving blowing as hard as you can) on your first visit. These tests are done routinely to rule out other causes of tiredness and breathing problems at night. Before you have your screening sleep study we will arrange for you to have some neuropsychological tests (tests of memory and concentration) and tests of sleepiness during the day.

The screening sleep study will tell us in most cases whether you have obstructive sleep apnoea or just simple snoring.

If it shows just snoring we will ask you to attend for a second visit in about a month for a second set of neuropsychological tests and tests of sleepiness. Your treatment for snoring will be arranged in the usual way.

If you have sleep apnoea we will ask you to have a full sleep study or polysomnography. This is the gold standard test to tell us how bad your sleep apnoea is and monitors the sleep stage, abdominal and chest movements, air flow, body position and oxygen saturation. We will also be using a technique called near-infra red spectroscopy to assess brain oxygenation during this study. This involves shining invisible (infrared) light about as bright as a torch beam across the head. By measuring changes in the light absorbed it is possible to estimate changes in brain oxygenation. The technique has been used for more than 10 years,and it has been entirely safe. You will have 2 leads attached to your forehead using a self adhesive sticker and a cloth band. Measurements are entirely painless, but occasionally the site gets a little red if the probe is on for a long time. There are no other side effects.
The following morning you will be given a continuous positive airway pressure machine (CPAP), to use until we finish the study (4-6weeks). This is the best treatment we know for obstructive sleep apnoea and can give benefit in even mild cases. After about a month you will have a second set of neuropsychological tests and

tests of sleepiness as well as a second polysomnography sleep study with the cerebral oxygenation measurements on CPAP treatment to see how you have improved.

If you have any questions either now or at any time please ask. Your participation in the trial is entirely voluntary and if at any time you wish to stop taking part you may do so. This will not affect your subsequent clinical care in any way.

You can contact the investigators, Dr Makker or Dr McGown, by leaving a message with the lung function lab (0207 380 9243) or on voice mail (0207 636 8333, ext 4135), and we will return your call as soon as we can.

All proposals for research using human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the Joint UCL/UCLH Committees on the Ethics of Human Research. All personal information, results and records of the study will be kept confidential.

Extra time needed for study

The neuropsychological tests and tests of sleepiness take about 40 minutes each. Sleep studies require an overnight stay in the Middlesex Hospital.

Summary of hospital visits required

Visit 1 (today) Sleep research clinic
Consent
Blood test, lung function test

Visit 2 (day) Neuropsychological tests
Tests of sleepiness

Visit 3 (night) Screening sleep study

Visit 4 (night) Polysomnography sleep study
(OSA only) Cerebral oxygenation measurement
Loan of CPAP machine

Visit 5 (day) Neuropsychological tests
Tests of sleepiness

Visit 6 (night) Polysomnography sleep study
(OSA only) Cerebral oxygenation measurement

Sample first appointment letter for prospective study

UNIVERSITY COLLEGE LONDON HOSPITALS

DEPARTMENT OF THORACIC MEDICINE
The Middlesex Hospital
Mortimer Street, London W1N 8AA

Laboratory

3

Hospital Number .....

Date.....

Dear

Thank you for agreeing to take part in our study on neuropsychological functions and brain oxygenation in obstructive sleep apnoea

Please can you attend the sleep study room on Campbell Thompson Ward at the Middlesex Hospital

On .....

At .....

Where one of the Sleep Technicians will be meeting you.

This appointment is for tests of sleepiness and tests of memory and concentration. It will take a maximum of 2 hours

Please try to avoid drinks containing caffeine (coffee, tea, cola) and alcohol on the day of the test.

You can contact the Sleep Technicians (Kerri or Kanta) by leaving a message in the Lung Function Laboratory (020 7380 9243) if you wish to change or cancel the appointment, or if you have any questions. We will return your call as soon as we can.

Occasionally due to pressure on beds, we are told to cancel day patients at the last minute. We will therefore ring you on the morning of the appointment if the room is not available. If you prefer you can ring us on the numbers above, any time after 9.30am

Yours sincerely

Dr H K Makker
Consultant Respiratory Medicine

Sample consent form for prospective study

UNIVERSITY COLLEGE LONDON HOSPITALS

DEPARTMENT OF THORACIC MEDICINE
The Middlesex Hospital
Mortimer Street, London W1N 8AA

TB Health Visitor

FAX

CONSENT FORM

STUDY OF NEUROPSYCHOLOGICAL DYSFUNCTION IN OBSTRUCTIVE SLEEP APNOEA

Have you read the information sheet about this study?	yes ☐	no ☐
Have you had an opportunity to ask questions and discuss this study?	yes ☐	no ☐
Which investigator did you discuss the study with?	.....	
Have you received satisfactory answers to all your questions?	yes ☐	no ☐
Have you received enough information about this study?	yes ☐	no ☐
Which doctor have you spoken to about this study?	.....	
Do you understand that you are free to withdraw from this study....		
*at any time	yes ☐	no ☐
*without giving a reason for withdrawing	yes ☐	no ☐
*without affecting your future medical care? (if relevant)	yes ☐	no ☐
Do you agree to take part in this study?	yes ☐	no ☐

Signature of patient/volunteer..... Date.....

Signature of investigator.....Date.....

Sample patient information letter for COPD study

ASSESSMENT OF CEREBRAL OXYGENATION USING NEAR-INFRARED SPECTROSCOPY

PILOT STUDY

You are being asked to take part in a study on brain oxygenation in chronic lung disease. At the moment prescription of oxygen depends on blood tests, but it is not completely clear where the cut off should be. It is possible that measuring brain oxygenation could help with this. Near-infrared spectroscopy (NIRS) is a technique which involves shining invisible (infrared) light about as bright as a torch beam across the head. By measuring changes in the light absorbed it is possible to estimate changes in brain oxygenation.

The technique has been used for more than 10 years mainly on special care babies and volunteers. You will have 2 leads attached to your forehead using a self adhesive sticker and a cloth band. Measurements are entirely painless but you will have to stay as still as possible for periods of about 15 minutes while we are recording. The whole study will take about an hour and you will be breathing air some of the time and 24% (controlled) oxygen some of the time. We will also be monitoring your oxygen saturation with a finger probe. Occasionally people find the leads a little uncomfortable, but not normally if the recording periods are less than 1 hour.

Your participation in the trial is entirely voluntary and if at any time you wish to stop taking part you may do so. This will not affect your subsequent clinical care in any way.

If the doctor looking after your lung disease wants you to have an arterial blood test we will do it at the same time as the trial. However we will not be doing any blood tests unless they are requested by the clinician looking after you.

Sample consent form for COPD study (printed on headed paper)

CONSENT FORM

ASSESSMENT OF CEREBRAL OXYGENATION USING NEAR-INFRARED SPECTROSCOPY

PILOT STUDY

Have you read the information sheet about this study?	yes ☐	no ☐
Have you had an opportunity to ask questions and discuss this study?	yes ☐	no ☐
Have you received satisfactory answers to all your questions?	yes ☐	no ☐
Have you received enough information about this study?	yes ☐	no ☐
Which doctor have you spoken to about this study?	.....	
Do you understand that you are free to withdraw from this study....		
*at any time	yes ☐	no ☐
*without giving a reason for withdrawing	yes ☐	no ☐
*without affecting your future medical care? (if relevant)	yes ☐	no ☐
Do you agree to take part in this study?	yes ☐	no ☐

Signature of patient/volunteer.....

Date.....

Signature of investigator.....

Date.....

Sample recruitment letter for COPD study

Dear

We (Dr Makker and I) are doing a pilot study on the use of near-infrared spectroscopy to measure cerebral oxygenation changes in patients with COPD who may require home oxygen, to see if the technique is likely to yield any useful information.

If you see anyone in clinic over the next few weeks (until end May1999) who you would like to have an ABG done on as a work up for LTOT (ie anyone with a saturation < 91% or so); or who is already on LTOT but you think might be willing to take part, please can you put them in contact with me (Anne McGown bleep 2015). I will give them an appointment for ABG and for an hour or so of NIRS if they agree.

I enclose a copy of the patient information sheet.

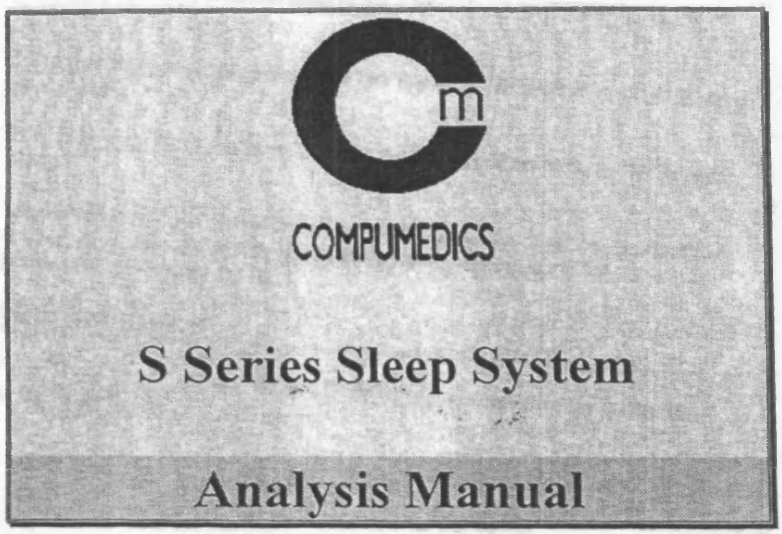
We have obtained ethical approval for this project.

Thank you for your help.

Yours sincerely,

Dr AD McGown

Relevant section of Compumedics manual referring to respiratory analysis



RESPIRATORY ANALYSIS

Introduction

The automatic respiratory analysis software on the S Series Sleep System system uses a period and peak to peak detection routine to identify abnormal respiratory patterns.

Channels Used

The default primary channel used is the Airflow (or CPAP if Airflow is not available).

The default secondary channels are the Thoracic and Abdominal Respiratory Movements.

These defaults can be altered from the Respiratory Parameters configuration menu.

The two secondary channels are analysed separately. These two channels are not summed, so there is no possibility of cancelling out if they are out of phase with each other by 180°.

Event Classification

Fig.1, Flowchart of Automatic Respiratory Analysis, briefly details how the events are classified.

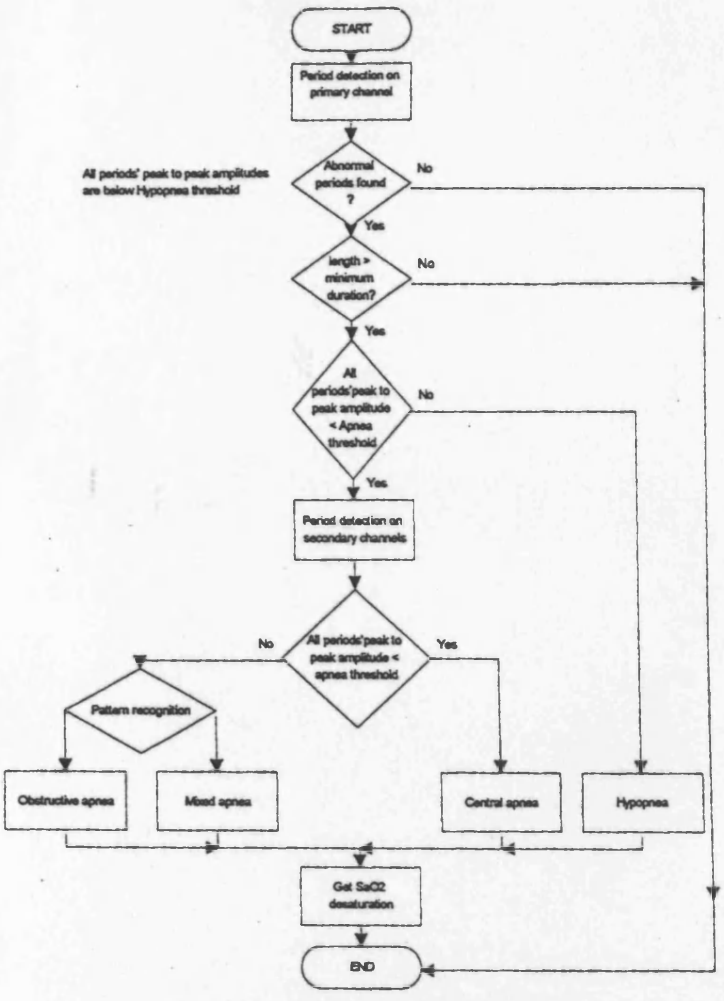


Fig.1, Flowchart of Automatic Respiratory Analysis